ANNUAL REPORT
OF
PROGRAM ACTIVITIES
NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE
FISCAL YEAR 1980
VOLUME I

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Public Health Service National Institutes of Health

ANNUAL REPORT of program activities,

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ANNUAL REPORT

October 1, 1979 through September 30, 1980

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Annual Report of the Director
# of the
National Institute of Neurological and Communicative Disorders and Stroke
October 1, 1979 through September 30, 1980

Since this will be my last report as Director, NINCDS, it seems appropriate to review the record of the eight years during which I have been Director, rather than simply taking cognizance of the one year just past. The period of this review covers FY 1973 through FY 1980, a period of many changes and events.

During that eight year period there were three Presidents of the United States (Richard Nixon, Gerald Ford, and Jimmy Carter); four Secretaries of DHEW (Casper Weinberger, David Mathews, Joseph Califano and Patricia Harris) and the change from DHEW to DHHS; four Assistant Secretaries of Health (Drs. Charles Edwards, Theodore Cooper, James Dixon [Acting], and Julius Richmond) with full restoration of the post of Surgeon General of the U.S. at the 0-9 rank; five Directors of NIH (Drs. Robert Marston, John Sherman [Acting], Robert Stone, Ronald Lamont-Havers [Acting] and Donald Fredrickson), as well as three Deputy Directors of the NIH (Drs. John Sherman, Ronald Lamont-Havers, and Thomas Malone) and three Deputy Directors for Science (Drs. Robert Berliner, DeWitt Stetten and Robert Goldberger). Also during the same period the National Institute of Aging was legislated, and the Directors of seven of the 11 research institutes at the NIH changed. Only NIAMDD, NINCDS, NEI and NIEHS had the same director for the entire period of my tenure at NINCDS. In addition there were changes at the NIH of the Directors of the Fogarty International Center, the Clinical Center, DRG, DFM, DPM and the NIH Associate Director for Administration.

Budget and Fiscal

Against this backdrop of considerable shifts in the staffing of the top Federal posts of relatively direct importance to the NIH and the NINCDS, there were comparable events and changes in the areas of the Federal budget and personnel. Early in this eight-year period, there was an "impoundment" of appropriated NIH funds by the Nixon administration in FY 1973, and the subsequent restoration of these funds in the following year with passage by the Congress of the anti-impoundment legislation. Nevertheless the Nixon administration made further attempts to rescind part of the NIH appropriations or to defer expenditures from them, in each case without success. One appropriation bill was vetoed by President Nixon but the veto was overridden by the Congress. In FY 1974 the existing Training Grants Program at the NIH was phased out by Secretary Weinberger. After a period of uncertainty the Congress authorized a substitute program, the National Research Service Awards (individual fellowships and institutional awards), but this measure did not permit funding of institutional research training resources to the degree possible under the former system and there were the additional constraints of requiring biennial (now triennial) re-authorizations by the Congress (with one prolonged delay) and imposing pay-back provisions on trainees.

The past eight years have witnessed increasing delays in the DHEW (and NIH) appropriations process. The shift of fiscal years from a July 1 beginning to an October 1 beginning in FY 1977 has not alleviated the problem. On several occasions we were well into the fiscal year (by three to five months) before we were certain of the level at which we could fund our research programs, and recently (FY 1978 and FY 1980) whole years were authorized under a Continuing Resolution--one major stumbling block being the increasingly bitter disputes over the anti-abortion funding amendments attached to all versions of the HEW/DHHS appropriations bills, and even to some continuing resolutions. The Congress was not the only source of uncertainties and problems, since the Office of Management and Budget became a major factor in the Nixon Administration and continues so today. Presidential budgets almost always sought to reduce future NIH budgets or to minimize any increases. In a period when inflation became an increasingly significant factor, the losses in NIH and especially NINCDS purchasing power assumed major proportions (Table 1). The Carter Administration introduced Zero Base Budgeting and this and other so-called planning exercises escalated in an extraordinary way the man-hours and paper-work devoted to many such relatively fruitless, indeed often meaningless, exercises. Recently the NIH has tried to present its needs in such modes as BAD (basic, applied and developmental research) and SATT (science base, application, technology transfer and training) and has introduced concepts of research grant "stabilization"--all attempts to defend its research funding base and to achieve some measure of assurance for future support. Unfortunately what were regarded as budget "floor" levels by the NIH often ended as budget "ceilings" in the OMB and the Congress.

The NIH is now faced with a new type of threat in the accountability and reauthorization legislative proposals contained in the currently pending Kennedy and Waxman bills (S988 and HR1073 - 96th Congress). For the NIH and most of its components to lose the broad authority of Section 301 of the PHS Act (as intended by the Waxman version) or to be subject to another level of control by monitoring and advisory board (in the Kennedy version), among many provisions, would seem definitely to impose unnecessary constraints on a most vigorous and successful enterprise. Most of the biomedical research community and former NIH officials agree. Already restrictive ear-marking amendments like that introduced by Congressman Walgren suggest some of the major problems to be anticipated if such proposed legislation should become law.

Personnel

Pari passu with such fiscal and budgetary events, the same eight-year period has been most difficult from a personnel staffing standpoint. We have lived almost continuously with personnel ceilings, freezes and cut-backs. For the NINCDS (Table 1) the problem has been especially severe. The NINCDS was unfairly penalized in the early 1970's by the attempts of OD-NIH to obtain termination of our Collaborative Perinatal Project (CPP) and to use the "liberated" personnel slots for our other needs. As a result, the NINCDS-FTP personnel ceiling dropped from 591 in FY 1971 to 515 in FY 1974, and it was only when I convinced then NIH Director Dr. Stone that the NIH provided no mechanism to dispose of the incumbent personnel in the CPP group, even if that activity were abolished, that the OD-NIH ceased attrition on the NINCDS personnel ceilings. Subsequent events, mostly beyond NIH control, have prevented any significant reversal of that disastrous decline.

In addition problems of recruitment and retention have multiplied. The NINCDS has experienced inordinately long delays in recruiting key personnel, such as chiefs for the Surgical Neurology Branch, the Laboratory of Neurophysiology, and the Medical Neurology Branch in the Intramural Program, and

Table 1
NINCDS-Budgetary Data FY 1973-FY 1980

Fiscal Year	Appropriation or Continuing Resolution	Constant 1974 Dollars	Percent of Approved Grants Funded	Personnel Budgeted	Positions Ceilings
1973	$107.4 M*	–	30%	–	557
1974	143.7 M†	[143.7]	57%	–	515
1975	142.5 M	[128.7]	64%	–	510
1976	144.4 M	[121.7]	34%	543	511
1977	155.5 M	[123.0]	27%	541	511
1978	177.0 M	[131.0]	53%	552	522
1979	212.4 M	[141.5]	60%	567	547
1980	242.1 M**	[147.5]	54%	551‡	528
1981	(House 253.8 M)	[139.6]	–	–	–

*Originally $130.6 M, with $23.2 M impounded.

†Originally $120.8 M, plus 22.9 M of impounded 1973 funds.

‡Distributed 324 to Intramural; 173 to Extramural; and 54 to Program Management.

**Breakdown as follows:

	Research Grants: Commitments (1001)	$76.8 M	
	Competing New/Renewal (506)	54.7 M	$131.5 M
	Research Centers (45)		27.2 M
	Research RCDA, etc. (191)		7.3 M
	Research Clinical Trials, etc. (27)		3.3 M
[68.8%]	(Subtotal)		(169.3 M)
	Training: Fellowships (195)	3.5 M	
[3.7%]	Institutional (301)	5.4 M	8.9 M
[7.0%]	Research Contracts		15.1 M
[10.5%]	(Subtotal)		(193.3 M)
[4.7%]	Intramural Research (plus 3.9 M contracts)		25.4 M
[4.7%]	Research Management (NINCDS)		11.3 M
[5.4%]	NIH Management Funds		13.0 M
	(Total)		(243.0 M)

directors for the Communicative Disorders Program and the Stroke and Trauma Program in the Extramural Programs. In most of these cases several years or more have been required and two posts (LNP and MNB) remain vacant today. Recruitment of physicians is particularly difficult because of the growing disparity between the Federal pay maximum and the academic and private practice incomes that average 50 percent to 100 percent or more higher.

These problems are compounded by the fact that reduced ceilings have deprived the NINCDS of adequate "executive" back-up personnel (in cases of resignation, retirement or death), as well as secretarial and technical support personnel, and intramurally clinical and research associate and staff fellow pools. With a maturing staff in the NINCDS and throughout the NIH, we contemplate a growing number of personnel that ought to be shifting to other duties or retiring. This is particularly evident in the intramural research areas, but the NIH has not planned for this problem and as yet can offer no solutions to a potentially very serious problem.

At the same time other complexities have surfaced. The Civil Service Reform Act passed by the Congress two years ago, has created the Senior Executive Service and Merit Pay Pool cohorts of Federal employees, but the initial promise of bonuses and awards and of flexibility in dealing with senior executives has not materialized. Instead these groups have been deprived of previously guaranteed rights like step and cost of living increases and have seen bonuses denied or curtailed capriciously. Moreover, the final decision on bonus awards and also on recruitment selections has been reserved to the Secretary--neither the original intent of the Act nor the most constructive managerial options. And the process demands an incredible amount of paper work and commitment of man-hours of top-level executives. I suspect that this whole personnel program may turn out to be one of the worst disasters ever to hit the Federal personnel system.

Concomitantly the Civil Rights-Affirmative Action initiatives have grown in numbers and importance. Obviously impositions of personnel ceilings, reductions and freezes, difficulties in recruitment and retention, and the Civil Service Reform Act are often hardly compatible with Affirmative Action and with its latest requirements in the FEORP (Federal Equal Opportunity Recruitment Program) mandates. Over the last decade the NINCDS has demonstrated a significant commitment to EEO-Affirmative Action-Civil Rights, and has been one of the leading components at the NIH in this respect. Some NINCDS staff recognized needs relatively early, so that the NINCDS was among the first to request an "ombudsman" and to institute "sensitivity" training sessions. Much of the credit goes to dedicated employees like Levon Parker (the NINCDS EEO Coordinator), [illegible], George [illegible]all, Jean Oliver, Fann Alexander and the NINCDS EEO Advisory Committee members and others. They have provided the Director and the NINCDS Executive Staff with the advice and support essential to the NINCDS program. There is still much to be accomplished, but with such dedicated personnel the prospects are promising.

The final element of personnel problems concerns the long record of delays in appointments to NINCDS advisory groups over the past eight-year period. Such delays have occurred in approvals and appointments of NINCDS Advisory Council members, members of the NINCDS Board of Scientific Counsellors, members of Congressionally-mandated Commissions (Multiple Sclerosis, Epilepsy, Huntington's Disease), and various advisory and review committees. Some of the delays [illegible] The NINCDS has been embarrassed by having to request Congress for extensions beyond the originally-specified life of each of the Commissions because of departmental delays in chartering and selecting members of the Commissions. Each Administration has tried to reduce the number of Federal advisory groups, consultants, etc. often with Congressional complicity, without regard for vast differences in the responsibilities and importance of such groups. In the NIH context this has been an extraordinarily short-sighted and counter-productive policy.

NINCDS Milestones

The period FY 1973 to FY 1980 saw the NINCDS pass two significant milestones, its 25th and 30th anniversaries. The 25th was marked by the publication of a three-volume work on The Nervous System, covering basic and clinical neurosciences and disorders of human communication, with contributions from a large number of NINCDS grantees. In 1977 one of our intramural scientists, Dr. Carleton Gajdusek, was awarded the Nobel Prize in Medicine for his discovery of the transmissible nature of the atypical slow virus disorders of the Kuru-Creutzfeldt-Jakob type. And Dr. Gajdusek and a fellow intramural scientist, Dr. Roscoe Brady, were elected to membership in the National Academy of Sciences. Leadership of the NINCDS was recognized by promotion of its two top administrators (Director and Deputy Director) to the flag rank of Assistant Surgeon General in the USPHS Commissioned Corps.

On a sadder note the NINCDS and the research community have lost some of its most valued and prestigious members. Dr. Pearce Bailey, first director of the Institute (1951-1959), died in 1976. Other losses have been: Dr. Ludwig Von Sallmann (first Chief of the NINDB Ophthalmology Branch); Dr. Michelangelo Fuortes (Chief of the NINCDS Laboratory of Neurophysiology); Dr. Kenneth Hisaoka (first Director of the NINCDS Extramural Activities Program); and in the community at large some special friends of the NINCDS: Professor H. Houston Merritt (of the New York Neurological Institute); Professor Wilder Penfield (of the Montreal Neurological Institute); Professor Raymond Carhart (of Northwestern University); Professor Jordi Folch-Pi (of the McLean Hospital neurochemistry research laboratory); and Professor Stephen Kuffler (of the Harvard neurobiology department). These are not exhaustive lists, but note some of the significant events.

NINCDS Reorganization and Staffing

The eight-year period under review saw a number of major changes in the administrative organization of the Institute and in the key personnel of its staff. During the 1973-1975 period most of the existing NINCDS Collaborative and Field Research division was absorbed into the Intramural Program (as the Infectious Diseases Branch under Dr. John Sever and the Laboratory of Central Nervous System Studies under Dr. Carleton Gajdusek) or to the Extramural Programs (contract operation) and OD-NINCDS (Office of Biometry and Epidemiology under Mr. William Weiss). During this same period there was serious consideration of reorganization of the Extramural Program of the Institute from its traditional organization based on mechanisms of support (research grants, training and contracts) to a programmatic mechanism. At that time every institute at the NIH except the NINCDS had effected such a reorganization; and the NINCDS had been under intense pressure, including two special evaluation studies, to follow suit. On the basis of a plan devised by Dr. Murray Goldstein, the reorganization to a programmatic mode was implemented in FY 1975, and coincidentally the name of the Institute was modified by Secretarial order from the National Institute of Neurological Diseases and Stroke (NINDS) to the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) to recognize more specifically its long-standing responsibilities for research on hearing, speech and language disorders.

The extramural reorganization of the NINCDS created four operational programs and a coordinating support program, in addition to the existing Intramural Research Program, for an organizational total of six programs. The four operational extramural programs were: the Fundamental Neurosciences Program (FNP), the Neurological Disorders Program (NDP), the Stroke and CNS Trauma Program (STP), and the Communicative Disorders Program (CDP), all coordinated and supported by the Extramural Activities Program (EAP) which comprised the activities of contract management, grants processing and management, scientific evaluation (from program project and center grants) and data analysis and reports. Initially the following respective staff were selected as Associate Directors of NINCDS to direct these programs: Drs. Karl Frank, Kiffin Penry, Murray Goldstein (Acting), Wesley Bradley, and Murray Goldstein. By FY 1980 this roster had undergone a complete turnover as a result of retirements, resignation or reassignment to give the current respective staffing of: Drs. Eugene Streicher, Floyd Brinley, Michael Walker, Ralph Naunton and John Dalton. The current distribution of NINCDS research investments among these programs is summarized in Table 2.

During FY 1976 these reorganizations were further consolidated by moving all extramural and related elements into the Federal Building in Bethesda--not an ideal situation but on balance a clearly constructive move. At the same time the research contract program was strengthened and given credibility in the biomedical research community by temporarily recruiting Dr. Mathilde Solowey to organize impeccable technical merit review policies and procedures and to act as ambassador to the community. It is fair to say that Dr. Solowey's presence and efforts, plus those of the NINCDS staff, proved most effective in gaining acceptance and confidence for our contract projects. At this time also the Office of Program Planning and Evaluation (OPPE) was created in the OD-NINCDS with the help of Dr. Leo Fox and Dr. George Murray was recruited to head that office.

Concomitantly a number of changes occurred in the NINCDS Intramural Program. Several new laboratories or branches were created: the Developmental and Metabolic Neurology Branch under Dr. Roscoe Brady, the Laboratory of Neuro-Otolaryngology under Dr. Jörgen Fex, the Neuro-immunology Branch under Dr. Dale McFarlin, and the Experimental Therapeutics Branch under Dr. Donald Calne. Drs. Fex and McFarlin were successfully recruited from Indiana and Emory Universities respectively. The incumbent Scientific Director, Dr. Henry Wagner, had asked to be relieved of his responsiblities to return to laboratory research, and after a diligent search Dr. Thomas Chase was recruited from NIMH to fill the post. He divided the intramural organization into two divisions: the Basic Research Laboratories Division directed by Dr. Richard Irwin, and the Clinical Research Branches Division directed by Dr. Donald Calne, who was recruited from Britain to be the first permanent NINCDS Clinical Director after a prolonged interregnum with acting clinical directors. With the increasing pace of studies on atypical slow virus infections the NIH and the NCI acceded to NINCDS and assigned a building at the Frederick Cancer Research Center (at Ft. Detrick in Frederick) to replace the facilities at Patuxent on loan from the USDA and to house high risk animal holding and tissue processing facilities. At about the same time two sections in the Laboratory of Biophysics were geographically moved to the

Table 2
Programmatic Distribution of Research Investments as of FY 1979

By NINCDS Program Areas (Percentage of total $242 M budget)

Communicative Disorders Program	13.9%	[17.9%]*)	
Neurological Disorders Program	32.3%	[41.6%]*)	- 77.8%
Stroke & CNS Trauma Program	17.4%	[22.4%]*)	
Fundamental Neurosciences Program	14.2%	[18.1%]*)	
Intramural Research Program	12.1%)		
NINCDS Program Management	4.7%)-	22.2%	
NIH Management Fund	5.4%)		

*Percentages of extramural total only.
Compare with Table 1 footnote ** for breakdown by support mechanisms.

By Representative Disorders (in $M)

Amyotrophic Lateral Sclerosis	$ 2.98 M.	
Autism	0.82	
Cerebral Palsy	23.18	
Deafness	26.9	
Dementias	5.29	
Diabetic Neuropathy	4.38	
Epilepsy	21.89	(Drug Development 3.26)
Huntington's Disease, etc	4.95	(Total Genetics 13.1)
Multiple Sclerosis	13.60	
Muscular Dystrophy and other Neuromuscular Diseases	15.38	
Parkinson's Disease	7.76	
Spinal Cord Injury	16.6	(CNS Regeneration 7.7)
Head Injury	5.7	(CNS Trauma total 22.3)
Stroke	20.74	
CNS Tumors	3.29	
Speech and Language Disorders	7.76	
Infectious and Immunological Disorders	38.8	

Marine Biological Laboratories at Woods Hole, Massachusetts on a full-time basis--a move designed to provide better access to marine species and to obviate the traditional yearly shifts back and forth. This satellite laboratory facility had an enthusiastic endorsement from the then NIH Deputy Director for Science, Dr. Stetten. These two off-campus facilities of the NINCDS were in addition to the existing research facility on Guam, concerned with the investigation of amyotrophic lateral sclerosis and Parkinson's disease-dementia especially prevalent among the Chamorro natives on that island. With the temporary termination of epidemiological capabilities within the NINCDS, administrative supervision of the Guam facility was shifted to the office of the Scientific Director, where it remains.

Several key intramural personnel changes have taken place in addition to those already mentioned. In the Surgical Neurology Branch, Dr. John Van Buren stepped down as branch chief, to be followed in an acting capacity by Dr. Ayub Ommaya and eventually succeeded by Dr. Paul Kornblith, recruited from Harvard-M.G.H. after a three-year search. More recently Dr. W. King Engel has stepped down as branch chief of the Medical Neurology Branch and has announced his acceptance of a post at the University of Southern California, Los Angeles. A search for his replacement is in progress, likewise a search for a new chief for the Laboratory of Neurophysiology following the untimely death of the incumbent, Dr. Michelangelo Fuortes. Nevertheless, as a result of reorganizations plus several key recruitments, clinical research and patient care within the NINCDS Intramural Program have improved very significantly and have overcome the negative image that had been prevalent in the OD-NIH eight years ago. Now with the imminent completion and opening of the NIH Ambulatory Care Research Facility there is much planning for utilization of the additional laboratory and clinic space for a new Communicative Disorders Branch (recruitment for a chief already in progress), as well as better facilities for existing clinical branches. In addition plans are well advanced for the intramural positron emission tomography (PET) program. Studies are already in progress with an existing imaging device and positron-isotopes obtained from neighboring facilities. A cyclotron for the NIH was ordered during FY 1980, and a site for its installation has been designated.

During the past eight years a number of important personnel changes have occurred. Not all can be tabulated here, but a few do deserve mention. Several long-time, key staff members retired or will do so shortly: Mr. Eckart Wipf as Executive Officer (succeeded by Mr. Paul Waugaman briefly and then Mr. Richard Sherbert); Mrs. Ruth Dudley as Chief of the Office of Scientific and Health Reports (succeeded by Ms. Sylvia Shaffer); Dr. Eldon Eagles as Deputy Director, NINCDS (succeeded by Dr. Murray Goldstein); Dr. Kiffin Penry as chief of the Epilepsy Branch (succeeded by Dr. Roger Porter) and later also director of the Neurological Disorders Program (succeeded by Dr. Floyd Brinley); Dr. Karl Frank as director of the Fundamental Neurosciences Program (succeeded by Dr. Eugene Streicher); Mr. Robert Sithens as Budget Officer (succeeded by Mr. William Matthews); Mrs. Lorraine Griffith as Secretary to the Director, NINCDS (succeeded by Mrs. Beverly Surles); Mr. Irving Nash as chief of Grants Management (succeeded by Mr. Edward Donahue); Mrs. Mollyanne Harris as head of Grants Processing (succeeded by Ms. Mary Burns); Dr. Malcolm Ray as chief of OPPE (with a search for his successor in progress) and Dr. Leo Fox as Associate Director of C&FR and Dr. Jan Cammermeyer as head of the Section on Experimental Neuropathology, LNNS. Other staff members have departed for other posts: Drs. John Van Buren and Ayub Ommaya from the Surgical Neurology Branch; Dr. Cosimo Ajmone-Marsan as chief of the Clinical Neurosciences Branch; Dr. Wesley Bradley as director of the Communicative Disorders Program; Dr. Jacob Brody as head of the Section on Neuroepidemiology (succeeded after an interval by Dr. Bruce Schoenberg); and Dr. George Murray as chief of OPPE. As I have noted in previous reports, despite the many staff changes the NINCDS has maintained its momentum in intramural research and in the support of extramural research and training. Unquestionably its ability to do so has depended upon the dedicated loyalty and exceptional abilities of the NINCDS staff, many of whom have decades of service and are leaders at the NIH in their areas of expertise. Finally we must not overlook the support provided by our external advisers. A partial listing, including the NINCDS Advisory Council and Board of Scientific Council members, is given in Table 3. To this list must be added the many who have served on study sections, project site visit teams, search committees, and more.

NINCDS Programs and Administration

One of the major developments during the FY 1973-1980 period was the appearance of Congressionally-mandated Commissions on specific diseases. There have been six such commissions imposed on the NIH, with three, including the first, directed to the NINCDS. The first was the National Commission on Multiple Sclerosis, authorized in 1973 and chaired by Mr. Charles W.V. Meares, with Dr. Harry Weaver as executive secretary. It was in many ways characteristic of later commissions; the Department procrastinated on approving a charter and on selecting commission members; and no resources for funding, housing or staffing the commission--all costs and personnel slots had to be provided by the NINCDS. The MS Commission gathered most of its data from a group of task forces and published a report containing a series of recommendations in 1974. Because of the nature and current status of the MS problem, emphasis was on basic research. Despite the level funding during that period (Table 1), the NINCDS was expected by the Commission and the Congress to increase its MS initiatives significantly. And even when it did so, the Institute was embroiled in agrument over whether some of these research initiatives were relevant to MS--a question settled in favor of the NINCDS by a special subcommittee appointed by the NANCDS Council. Some of the initiatives involved funding additional clinical research centers, conducting an epidemiological survey in the high prevalence focus of the Orkney and Shetland Islands, organizing a delegation to the Soviet Union, and emphasizing immunological research. During FY 1980 the FDA Bureau of Biologics, the NINCDS and the National Multiple Sclerosis Society were confronted with the snake venom treatment claims from a pair of Florida promoters and subsequent Congressional pressures to do something about it. The MS Society-generated research grant application for clinical trials was not approved by the NANCDS Council and at the end of calendar 1980 the ethics of the venom producer and the safety of the venom preparation are in considerable doubt, with litigation pending. It seems to us that any trials under these circumstances would be unwise.

A second Commission on Diabetes was authorized in 1975, with involvement of most NIH institutes including NINCDS. The primary thrust of the recommendations for the NINCDS was concerned with research on diabetic neuropathy, and several research centers and a number of research grants are now in progress, despite the paucity of experts in this area and indeed in neuropathies in general. A training initiative was promoted. Somewhat to our surprise the Commission and its progeny, the Diabetes Advisory Board, have disregarded the equally important problem of diabetes as a major risk factor for stroke.

Table 3

NINCDS Advisory Council and Board of Scientific Counsellors FY 1973-1980

NINCDS Council (increased from 12 to 16 members in 1975)

Dr. Bobby Alford
Dr. Edward Boldrey
Dr. Harold Booker*
Dr. Patrick Bray
Dr. Mary Brazier
Dr. Theodore Bullock
Dr. Calvin Calhoun
Mrs. Dorothy Caram
Dr. Sidney Carter
Dr. Frank Cooper
Mrs. Marie Daniel
Dr. Calvin Early+
Dr. Lyle French
Mrs. Isabelle Goldenson
Dr. Sidney Goldring
Mrs. Ellen Grass
Dr. William Hardy
Ms. Myrma Hernandez
Dr. Warren Huber*
Dr. Geza Jako
Dr. George Koelle
Dr. Thomas Langfitt
Dr. Merle Lawrence
Dr. Marjorie Lees

Dr. David Lim
Ms. Anita Smith Lunsford
Dr. Guy McKhann
Mr. Charles Meares
Dr. Paul Moore
Dr. Lois Moreland
Mr. Delyte Morris
Dr. Michael Okihiro
Dr. Michael Paparella
Dr. Sidney Peerless
Dr. Fred Plum
Dr. Bronson Ray
Dr. Edward Richardson
Dr. Augustus Rose
Dr. Peritz Scheinberg
Dr. Richard Schmidt
Mr. David Scott (resigned)
Ms. Jennifer Jones Simon
Dr. George Sisson
Dr. James Snow
Dr. James Toole
Ms. Cleo Wallace
Dr. Arthur Ward

NINCDS Board of Scientific Counsellors

Dr. Richard Barringer
Dr. Robert Bourke
Dr. Jennifer Buchwald
Dr. James Ferrendelli
Dr. Eli Goldensohn
Dr. Ann Graybiel
Dr. Rita Guttman
Dr. Donlin Long
Dr. Loren Mullins

Dr. Eugene Roberts
Dr. Lewis Rowland (C)
Dr. Francis Schmitt
Dr. Marian Smith (C)
Dr. Oscar Sugar
Dr. Kumihiko Suzuki
Dr. Robert Terry (C)
Dr. Leonhard Wolfe
Dr. Harry Zimmerman (C)

*Veterans Administration representative
+Department of Defense representative
(C)Chairman of the Board

The other two Commissions involving the NINCDS were authorized in 1975 and established a year later for Epilepsy and for Huntington's Disease and Related Disorders. The Epilepsy Commission was chaired by Dr. David Daly initially and later by Mrs. Ellen Grass with Mrs. Patsy Owens as Executive Secretary; and the HD Commission was chaired by Mrs. Marjorie Guthrie and Dr. Nancy Wexler as Executive Secretary. On the basis of prior experience with the MS Commission, the NINCDS was able to do a much better job of staffing and supporting these Commissions, and there was much better appreciation by the commissions of the Institute's needs and problems. Both commissions held a number of public hearings and developed recommendations that addressed both research and patient care and services problems. Some of the improvements in the NINCDS fiscal picture in recent years reflect the impact of these Commissions and their reports on the Congress. Two major initiatives, among many, were emphasized by the Epilepsy Commission: the anticonvulsant drug screening and development program and the epilepsy comprehensive center program. The final award in the latter program took place in FY 1980 with selection of UCLA for an urban comprehensive center. The HD Commission insisted on attention to related neurogenetic and degenerative disorders and argued strongly against creation of any more commissions. Several major recommendations have been implemented in FY 1980 with the award of two Centers Without Walls and the conclusion of negotiations for studies of the HD focus in the Lake Maracaibo region of Venezuela.

It is appropriate to note here the continuing dialogue which the NINCDS maintains with the voluntary health agencies and the professional societies concerned with the neurological and communicative sciences and disorders. These groups total some 80 or more and can be a potent force in making our collective messages heard. A majority of the groups are amalgamated by membership in the independent National Committee for Research on the Neurological and Communicative Disorders, one of the principal forums in which interactions between NINCDS and lay and professional groups can occur. In addition the NINCDS has recently sponsored meetings with some or all of these groups at the NIH in Bethesda in the interests of public relations and information exchanges. Since the first such public forum in 1975 these meetings have been enthusiastically received and have proved most constructive.

A number of other programmatic and administrative developments deserve brief mention. The NINCDS Collaborative Perinatal Project conceived and initiated in 1960 entered its final phase of data analysis and evaluation and the preparation and publication of monographs of such results. This phase is nearing completion; the CPP staff has gradually diminished as unneeded talents were dispersed elsewhere; and the remaining group has been redirected to research projects in developmental neurology. Contrary to the negative views of many a decade ago, the CPP has proved to be a most valuable body of data with facets not anticipated earlier in the project. Despite the multimillion dollar cost over 20 years, this has been a uniquely important study. With the data now stored on computer tapes it is available to qualified investigators for future research needs.

Likewise, the neurological information network launched in the mid-1960's came under critical scrutiny, and by the end of 1979 was largely terminated in terms of its original form. By FY 1973 only three major components remained. The Communicative Disorders Information Service located at Johns Hopkins Medical School was closed out in 1974 without much community impact. Initial attempts to close out the Brain Information Service (for basic neurosciences) located at the UCLA Brain Research Institute met with intense lobbying with the Congress and resulting directives to continue this activity. The Institute was confronted with a real dilemma: an increasingly expensive operation serving a relatively small subscribership and supported by a sole source contract over many years (no competitive renewals) and publishing bibliographies and reviews in violation of newer Government Printing Office regulations. Gradually the NINCDS was able to re-assert a measure of control over this activity and on advice of its advisors (especially the Scientific Information Program Advisory Committee) reduced the budget and focussed more sharply the products for publication. Meanwhile NINCDS staff had developed and began testing a citation program for the communicative disorders in collaboration with the National Library of Medicine. Congressional views began to change and directed the NLM and the NINCDS to review the Brain Information Service--a review which clearly underscored the fact that there were more sophisticated means of achieving the same goals more efficiently and at less cost, namely, custom bibliographies and abstracts tailored to individual investigator needs from country-wide computer terminals connected to the NLM data base. A neurosciences citation program was developed with the NLM to facilitate such a process and was substituted for the Brain Information Service in January 1980, with enthusiasm from scientists and no significant repercussions from the vested interests. The third service, the Clinical Neurological Information Service operated from the University of Nebraska also ended in 1980 as a result of the retirement of its dedicated director, Professor Walter Friedlander, after a highly successful service to the community. Plans are in progress with Professor Friedlander's consultation to adapt the neuroscience citation program to the needs of the clinical neurologist.

The NINCDS has continued to take stock with its advisors and consultants of program directions and needs. Manpower surveys in the areas of neurology, neurosurgery, otolaryngology, audiology and speech pathology, and the basic neurosciences were contracted for and completed by FY 1975--a particularly timely event in view of the needs for information on training needs as part of the new NRSA training legislation. The NANCDS Council initiated an examination of long-range research strategies for the next decade and the reports and recommendations were submitted and published late in 1979. This initiative involved seven panels (Communicative Disorders chaired by Dr. Paul Ward; Stroke and CNS Trauma chaired by Dr. Fletcher McDowell; Developmental Neurology chaired by Dr. Philip Dodge; Convulsive and Neuromuscular Disorders chaired by Dr. William Landau; Demyelinating and Sclerosing Disorders chaired by Dr. Richard Johnson; Pain chaired by Dr. Kenneth Casey; and Behavior chaired by Dr. Norman Geschwind) and two task forces (Basic Research chaired by Dr. Dominick Purpura; and Epidemiology and Statistics chaired by Dr. Alan Leviton). The recommendations developed by these groups have been adopted as guidelines for future planning by program staffs, and the budgetary and manpower resources recommended have been helpful for NINCDS discussions with Congressional Committees about projections of future needs.

A major initiative over the last five years in research on central regeneration, particularly with reference to spinal cord injury and paraplegia, developed from the growing recognition that the dogma of no central regeneration was no longer tenable. The NANCDS Council appointed in 1975 a task force which organized workshops, from which a summary report was prepared and published. Research on central regeneration became a special initiative which by FY 1981 will operate at about $9M. Much interest arose over Soviet reports of regeneration following enzyme therapy. The NANCDS Council dispatched Dr. William Windle to Yerevan in Soviet Armenia to evaluate the Soviet claims and to bring back the monograph published there. This he did and on the basis of these observations the Soviet investigator was invited to come to the United States to discuss his work. After some delay a Soviet delegation did come and discussed their work with the directors of NINCDS-supported Spinal Cord Injury Research Centers. Despite our skepticism the Soviet studies were repeated precisely under an NINCDS contract with completely negative results, apparently because the Soviet technique failed to achieve complete transection. At present the central regeneration initiative is concentrated on the twin questions of whether the long cerebro-spinal tracts do in fact demonstrate axonal outgrowth after transection and what the trophic and tropic mechanisms are which would ensure functional reconnections of regenerating fibres with appropriate target cells.

Other special initiatives: Incidence and Prevalence Surveys were undertaken under contract for the NINCDS Office of Biometry and Field Studies for multiple sclerosis, stroke, head and spinal cord injury, brain tumors, and epilepsy. In addition our OBFS has embarked on the development of data banks for stroke and for coma aimed at developing patient profiles for diagnostic, clinical management and prognostic purposes. After the enormous success of computerized tomographic head scans in clinical neurological management, the development of positron emission tomography (PET) assumed very special significance as a research tool for examining function and metabolic activity in the intact experimental animal and human nervous system. Neurochemical, neuroimmunological and neuropharmacological possibilities were particularly intriguing. The NANCDS Council and the Institute staff examined the potentials of PET and as a result embarked on a special research initiative, issuing a Request for Applications and subsequently funding eight centers at an initial level of $10M in the 1978-79 period. Already existing preliminary observations are emerging in increasing numbers. The future potentials in these areas appear very promising indeed.

In June 1976 the NINCDS was designated by the World Health Organization as one of its Collaborating Centers for Research and Research Training in the Neurosciences. Both Dr. Murray Goldstein and I plus a few other staff members (Drs. Penry, Schoenberg, Chase and Porter) have devoted considerable attention to the potentials offered in this program. Initially there were a number of meetings in such places as Abidjan (Ivory Coast), Marseille, Geneva, Firenze, Montreal, Lima, Ibadan (Nigeria), and Dakar (Senegal), plus trips to Egypt, India, and the People's Republic of China to evaluate potential additional collaborating centers--many of which have now been designated. More recently collaborative programs have been developed for neuroepidemiological studies in Nigeria, anticonvulsant drug pharmacokinetics in various ethnic and cultural settings, experimental therapy of diabetic neuropathy, and development of protocols for treatment of epilepsy and stroke in developing countries. In addition the NINCDS has initiated a Neurosciences Fellowship Program for nominees from developing countries to obtain specialized clinical training in the United States. The Fogarty International Center handles the administrative details of this program for the NINCDS. Fellows from Nigeria, the Philippines, Mexico and the People's Republic of China are already in training at the NINCDS or elsewhere in the United States. There have been many frustrations with this W.H.O. Collaborative Centers program but we believe that on balance there is much of potential benefit to the needs of the NINCDS as well as the needs of developing countries.

The past eight years have seen additional studies, workshops or initiatives concerning cerebral death criteria, chiropractic and spinal manipulation, psychosurgery, autism, dementias, cochlear (or auditory) implants, Reye's syndrome, slow and latent viruses and neuropeptides, as well as periodic reviews with participants in the NINCDS neural prosthesis program, and the directors of NINCDS stroke, head injury, spinal cord injury and comprehensive epilepsy center programs. Clinical trials are both necessary and often expensive. The NINCDS has continued to engage in a modest number to evaluate new anticonvulsive drugs, to evaluate measures for treating secretory otitis media and to study the natural history and implications of transient ischemic attacks. Two large trials are currently underway: one is to evaluate the extracranial-to-intracranial arterial anastomosis for transient ischemic attacks and stroke, with some 65 clinics in 11 countries participating in a 5-year prospective study; the other is to evaluate plasmapheresis as a treatment for acute Guillain-Barré syndrome, with some 25 clinics in several countries participating.

Finally there are a number of related issues that have impinged and continue to impinge on NINCDS programs and their administration. Among the most important have been the growing constraints on human experimentation emerging from the National Commission for the Protection of Human Subjects. Additional problems have been posed by the Freedom of Information and Privacy Acts; the reports of the President's Biomedical Research Panel; the Secretary's Health Research Planning Principles; the consensus development program of the NIH Office of Medical Application of Research and the recent extension into the National Institute for Technology Assessment; the problems of new drug clearances by the FDA and the growing issue of orphan drugs; trans-NIH and trans-Agency issues in nutrition, genetics and diabetes; recombinant DNA guidelines; and the results of the NIH Peer Review Committee deliberations. The last item has markedly modified the secondary review process for research grants at the advisory council levels, as a result of release of study section summary sheets including priority scores and the appeals generated therefrom for staff and council review. As could be expected all such matters have markedly escalated the paper work and staff time required to deal with them.

Research Developments--Examples

It is not possible in an eight-year overview of this sort to do justice to all the research developments which have taken place during that period. The following listing serves to exemplify the rich variety and burgeoning activity across the entire field of NINCDS responsibilities.

Neurotransmitters: details of synaptic vesicles; mechanisms of transmitter release and the role of calcium ions; studies of synapses with scanning and freeze-fracture electron microscopic techniques; axonal transport including uptake of nerve growth factor, viruses and toxins; receptor isolation and pharmacology with agonists and antagonists; opiate receptors and enkephalin and endorphin transmitters, with roles in pain, drug addiction and behavior; modulation of synaptic activity and relevance of the neuroendocrine systems; and the growing array of neurotransmitters numbering more than 30, perhaps as many as 50.

Neuroimmunology: isolation of receptor proteins and studies with antibodies thereto; animal models of myasthenia gravis and its recognition as an autoimmune disorder; circulating acetycholine receptor antibodies in myasthenia, the role of the thymus and therapy with immunosuppressants (Prednisone) or plasmapheresis; myelin-associated glycoproteins; HLA profiles and the role of T- and B-lymphocyte systems; oligoclonal antibodies; transfer of experimental allergic encephalomyelitis from one animal to another; twin-studies in multiple sclerosis; use of hybridoma techniques for production of specific pure antibodies (e.g. measles proteins); and gangliosides as receptors for cholera toxin.

Neurovirology: recognition of slow and latent viruses (SSPE in measles; herpes in sensory ganglia); tumors from Papova viruses; studies on the genetics of vesicular stomatis virus replication and the role of defective infectious particles; electron microscopic studies of viral replication; persistence of atypical slow viruses (scrapie, kuru, etc.) in formalin-fixed specimens and iatrogenic infections (from corneal transplants, implanted electrodes, etc); and tissue culture studies demonstrating circulating antibodies in Creutzfeldt-Jakob disease.

Neurogenetics: putative enzyme or transmitter abnormalities in inherited ataxias, dystonias, Huntington's disease and Alzheimer's disease; enzyme replacement therapy in Gaucher's disease and other sphingolipid storage diseases; experimental modification of the blood-brain barrier; modification of enzyme molecules to increase specificity of delivery and uptake.

Regeneration and Plasticity: recognition of several growth factors; demonstration of central regeneration in hippocampus; regeneration with embryonic implants; Schwann cell nerve graft studies peripherally and centrally; neural prosthesis development program.

Circulation: autoregulation of local circulation; studies on ischemia in stroke and trauma; the gerbil as an experimental stroke model; deficiencies in reperfusion after cerebral vascular occlusions; vasogenic and cytotoxic types of cerebral edema; monitoring of intracranial pressure; ultrasound evaluation of carotid patency.

Neuropharmacology: standardization of determinations of anticonvulsant drug levels; introduction of three new anticonvulsants (carbamazepine, clonazapam and valproate); evaluation of cerebellar stimulation for movement disorders; development of anticonvulsant drug screening and development program; brain tumor biopsies in tissue culture and evaluation of responses to chemotherapy; development of new drugs for Parkinson's disease (ergot derivatives: bromocriptine; lisuride); prednisone treatment for myasthenia gravis, polymyositis, dermatomyositis, etc.; plasmapheresis treatment for myasthenia gravis and possibly Gullain-Barré syndrome and multiple sclerosis; steroid high dose trials in CNS trauma; aspirin as a prophylactic measure against stroke.

Hearing, Speech and Language: specific evaluations of measures for treating secretory otitis media (tympanostomy tubes, decongestants, etc.); alternate approaches to communication with autistic children; newer techniques for treating aphasia; evaluation of disorder of language acquisition and speech development in pre-school children; new techniques for studying speech mechanism (X-ray microbeam); cochlear implant prosthesis developments; sensory input mechanisms and central processing.

In addition to the specific examples just cited, cognizance must be taken of the emergence of important new neuroscience disciplines over the past eight years: neurovirology, neuro-immunology, neuropharmacology, neuroepidemiology, and neuroendocrinology. Research on and development of neural prosthesis is another new discipline. And neurotoxicology is about to be added to this list as one of the most important areas for research on mechanisms and on clinical monitoring and detection techniques.

Envoi

In trying to gain an overall perspective of the eight-year record which I have tried to review here, one is impressed by two principal themes: the fiscal paradoxes and the unique priorities for research on the nervous system and its disorders.

About six years ago Eric Sevareid commented on the last major speech made by DHEW Secretary Weinberger. The Secretary pointed out that if social programs continue at the same rate for the next 20 years they will cost more than one-half of our entire Gross National Product (i.e., all the goods and services produced in this country). Sevareid commented that we lack a method of deciding what programs to keep and what to throw away; that the nation needs a balance sheet that it can understand. And he reminded us of the warning by John Stuart Mill that, in time, the good done by charity to its recipients would come into collision with the general good.

Indeed in FY 1980 the budget for DHHS accounted for some 35 percent of the entire Federal budget, the single largest item in that budget by far. Of the DHHS total, 95 percent goes to non-controllable entitlements of Social Security, Medicare, etc. and only five percent to discretionary items like health research. It is sobering to realize that total health costs in the United States, as estimated by Dr. William Walsh, exceed $220 billion per year, which translates to a rate of expenditure of $610 million per day or more than $20 million per hour. This rate is nearly 70 times the rate at which the entire NIH is supporting research, and about 1000 times the rate of NINCDS expenditure. Yet at least 20 percent of all Americans are significantly touched by neurological or communicative disorders, and the disabilities are chronic and severely debilitating, diminishing greatly the quality of life for these people. The costs to our society are enormous--in excess of $65 billion per year just for neurological and communicative disorders alone. We currently spend less than 0.4 percent of that amount for research on the understanding and the prevention or treatment of those disorders. Is this not a balance sheet that a nation can understand? Is it not obvious that an increased investment in research is essential to redress the present imbalance and to begin to reduce the enormous burdens presently imposed by these disorders?

In the conclusions of the President's Biomedical Research Panel published in 1976 they emphasized:

> "Perhaps the ultimate challenge to biomedical research, representing the very pinnacle of our understanding of the human organism, lies in neurobiology: how the brain and the nervous system develop, how they function in health and disease, how thought occurs, how memory is stored, how we reason, how we are motivated, and how we interact with our physical and social environment.

> "We hope that man will one day have a better understanding of himself and live more harmoniously with his fellow man. Thus, the study of brain and mind deserves greatly increased attention--from the many different disciplines of biomedical and behavioral science, as well as such fields as mathematics, linguistics, and the communicative sciences. This Panel commends neurobiology as a compelling long-range interest worthy of national attention."

And consider also a recent comment by Dr. Lewis Thomas:

> "Our most spectacular biological attribute, which identifies us as our particular sort of animal, is language, and the deep nature of this gift is a mystery."

Finally let me recall the experiments by psychologist Dr. Donald Hebb, who subjected human subjects to total deafferentation--deprivation of all sensory input. Such subjects rapidly veered to violent psychotic reactions.

What these excerpts or examples emphasize is the unique and central importance of the human nervous system--in health and life, in our human endeavors on this earth. Mission for the NINCDS is here. In these past eight years the mission has been vigorously and rewardingly addressed by staff, advisors, grantees, contractors, trainees and the community as a whole in a remarkable symbiosis. May it continue to flourish!

ANNUAL REPORT
October 1, 1979 through September 30, 1980
Equal Opportunity Office
Office of the Director
National Institute of Neurological and
Communicative Disorders and Stroke

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) affirmative action and civil rights activities are centered in the Equal Opportunity Office. The Office serves as principal advisory to the Director of the Institute and NINCDS managers at all levels concerning positive application and vigorous enforcement of Affirmative Action and Civil Rights policies of the Federal government. The Office is responsible for coordinating and monitoring the NINCDS responsibility in the enforcement of the 1964 Civil Rights Act in matters concerning its contracts and grants. The Office also coordinates the NINCDS Community Outreach Programs pertaining to increasing the representation of minorities and women in biomedical research, particularly the neurosciences.

The Federal Equal Opportunity Recruitment Program (FEORP), a provision of the Civil Service Reform Act of 1978, requires each Federal agency to conduct a continuing program for the recruitment of minorities and women to eliminate their under-representation in various job categories in Federal employment. Vigorous affirmative action recruitment and placement efforts will continue to be used by the NINCDS to correct under-representation of minorities and women in its work force ; therefore, the development and implementation of affirmative action and FEORP goals will be a major program initiative of the NINCDS in FY'81.

Personnel and Resources

Ms. Vivian A. Betton was appointed to the position of Equal Opportunity Specialist, OD, NINCDS, on April 20, 1980. In this capacity Ms. Betton will assist the Institute's Equal Opportunity Coordinator in the initiation, development and implementation of the NINCDS Affirmative Action and Civil Rights Programs. The Institute also has an Equal Employment Opportunity (EEO) Advisory Committee to the Director, an EEO Counselor that provides guidance and counseling to aggrieved employees and applicants who believe they have been discriminated against and a representative for the Federal Women's Program.

Significant NINCDS Affirmative Action Accomplishments and Initiatives in FY'80 were:

Recruitment and Placement

A minority male was appointed Deputy Director, Extramural Activities Program.

A minority male was selected for the position of Grants Management Specialist in the Grants Management Branch.

A woman was appointed Administrative Officer for the Extramural Activities Program.

Two women (minority and non-minority) were appointed Budget Analyst in the NINCDS Financial Management Section.

Two minority women were selected for training positions in the areas of EEG Technician and Contract Specialist.

A minority woman was selected for an administrative training position in the NINCDS under the NIH Stride Program (a training program with American University).

A minority male was appointed as a Personnel Management Specialist in the NINCDS Personnel Office.

A minority male was selected for the position of Computer Systems Analyst in the Office of Program Planning and Evaluation.

Community Outreach

Ms. Nyrma Hernandez, Deputy Executive Director for Program Services, Epilepsy Foundation of America Dr. David Lim, Professor of Otolaryngology and Anatomy, Ohio State University College of Medicine and Dr. Lois Moreland, Professor and Chairperson, Department of Political Science, Spelman College were appointed to the National Advisory Neurological and Communicative Disorders and Stroke Council.

Minority Biomedical Support Program projects from South Carolina State College, Texas A & I University, University of Hawaii and University of New Mexico were approved for funding by the NINCDS National Advisory Council.

The NINCDS will provide funds to support a National Conference of Hispanics and Native Americans in Science that will be held this fall.

Through the Summer Extern Program at Provident Hospital in Baltimore, Md., nine medical students from Meharry Medical College, Tennessee were selected for one-month assignments in the NINCDS.

The NINCDS participated in the following conferences, workshops and symposiums to help promote the advancement of minorities and women in the neurosciences:

a. The Minority Biomedical Symposium in Atlanta;
b. The National Urban League in Chicago;
c. A Hispanic Recruitment Conference in San Juan, Puerto Rico;
d. Blacks in Government (BIG) in Washington, D.C.;
e. Minority Access to Research Careers Program Directors' Meeting in Anaheim;
f. The National Medical Association Conference in Detroit; and
g. Career Planning and Job Fairs at Howard University, D.C. Public Schools and a career conference at the San Diego Convention Center.

The NINCDS awarded $32,000 to support 16 students participating in the Summer Research Apprenticeship Program for Minority High School Students.

The Institute continues to make significant progress in the recruitment and placement of minority undergraduate, graduate and medical students in the NIH Summer Employment Program. Fifteen minority medical students and twelve minority undergraduate students were selected for summer positions in the Institute's research laboratories.

Training

In February the NINCDS implemented an affirmative action training program for all NINCDS supervisors and managers. Approximately 90 (91%) took the training which focused on areas concerning affirmative recruitment, hiring, promotion, responsibilities of supervisors/managers in affirmative action, etc.

Awards

NINCDS Equal Opportunity Special Achievement Awards were presented to Dr. Paul L. Kornblith, Chief, Surgical Neurology Branch, Dr. Barry H. Smith, Medical Officer, Surgical Neurology Branch and Ms. Jean G. Oliver, Speech Pathologist, Neurological Disorders Program for their remarkable accomplishments and contributions to the development and implementation of affirmative action programs in the NINCDS.

Special Activities

Dr. Benjamin Osuntokun, professor of neurology at the University of Ibadan, Nigeria,is working on a pilot project with Dr. Bruce Schoenberg, Chief of the NINCDS Neuroepidemiology Section to study neurological disorders in Nigeria.

Deficiencies

The NINCDS FY'81 FEORP and Affirmative Action Programs will address the following areas to help correct under-representation of minorities and women in its work force.

a. Recruitment and placement of minorities in the Staff Fellowship, Clinical Associate and Research Associate Programs.

b. Increasing the number of minorities in the Biology, Chemistry, Microbiology and Information Specialist job series.

c. Ways to increase communication and awareness of NINCDS programs and activities to minority and women health professionals, communities and the general public.

d. Increasing the representation of minorities and women in grades 9-12, 13-15, and 16-18 including the Commissioned Corps.

e. Additional funds to support the Minority Biomedical Support Program and;

f. Additional minority personnel in administrative officer positions, particularly in the Intramural Research Program area.

NIH EEO Program

On January 21, 1980, the Director, NIH, Dr. Donald S. Fredrickson, created a Task Force to assess the mission, functions, and operations of the NIH Division of Equal Opportunity. Dr. Donald B. Tower, Director, NINCDS, and Mr. James S. Alexander, Equal Opportunity Coordinator, Clinical Center were selected as co-chairpersons of the Task Force.

Dr. Fredrickson charged the Task Force "to take a hard, deep look at the NIH Division of Equal Opportunity (DEO) and to come up with recommendations and creative ideas that will make the NIH-DEO a symbol and model for the government". The Task Force presented its report to the Director, NIH, on July 31, 1980.

Finally, action is needed at the DHHS or OPM level to eliminate barriers that impact on the ability of Federal agencies to achieve certain affirmative action goals, e.g., the OPM's register is closed from nine to ten months out of a year for biology, chemistry and microbiology positions, reductions in personnel ceiling, employment freeze, downgrading and the use of the PACE examination for external recruitment.

ANNUAL REPORT
October 1, 1979 through September 30, 1980

Office of Scientific and Health Reports
Office of the Director
National Institute of Neurological and Communicative Disorders and Stroke

National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) public information activities are centered in the Office of Scientific and Health Reports (OSHR). OSHR advises the Director and executive staff on the effective interpretation and reporting of Institute-conducted and supported research. This research is of interest and concern to many audiences, including Congress, the Department and other Government agencies, scientists, physicians, voluntary health agencies, patients and their families, and the general public.

OSHR consists of two sections: Public Inquiries and Publications. The Office deputy chief, newly appointed this year, develops and maintains contacts with reporters and freelance writers to interest them in stories about NINCDS research programs.

Coordinating the NINCDS research program with the programs of more than 50 private voluntary agencies and some 35 professional societies is a major OSHR function. One member of the Publications Section has been identified as OSHR liaison with the voluntary agencies, and works closely with them to determine their information needs.

This year, a new project was undertaken to increase the voluntary agencies' understanding of the NINCDS and its programs. In small workshops sponsored by the NINCDS Neurological Disorders Program, representatives of the voluntaries came to the NIH campus for a day and a half to tell Institute staff members about their agencies and to learn more about research under way at NIH and at grantee institutions. At these workshops, OSHR staff members described their work and had a chance to meet privately with representatives of voluntaries concerned with specific disorders. Three such workshops were held this year, and more are planned.

As a result of needs identified in these workshops, several NINCDS publications are being revised and new ones developed. The smaller agencies seemed to profit from the OSHR's presentation on ways to use the media to gain understanding of neurological disease and support for research. OSHR staff members continued to share ideas with workshop participants even after they had returned to their home offices.

Two cooperative efforts with voluntary agencies deserve special mention. With the arrival of the play "The Elephant Man" at the Kennedy Center in February 1980, an opportunity was available to disseminate information about neurofibromatosis--the neurological disease that afflicted the Elephant Man, John [recent research has shown his name was Joseph] Merrick. The OSHR deputy chief secured television coverage of the NIH neurofibromatosis clinic, and placed a feature article about neurofibromatosis in THE WASHINGTON STAR. Neurofibromatosis research gained national attention when Philip Anglim, who starred as the

Elephant Man on Broadway and on tour, appeared before the House Appropriations Subcommittee to seek increased funding for brain and nervous system research. His testimony was widely reported, thanks to wire service stories that appeared in many U.S. newspapers. As FY 80 ends, we await the premiere of Mel Brooks' film version of "The Elephant Man," and anticipate more opportunities for informing the public about research efforts to conquer neurofibromatosis.

In another major cooperative effort, OSHR has assumed responsibility for publicizing the first international symposium on Tourette Syndrome. This symposium, co-sponsored by the NINCDS, the Tourette Syndrome Association, and the Gateposts Foundation, will be held in New York City in May 1981. OSHR has placed a call for papers in major professional journals, and staff members will distribute flyers at professional meetings, announcing the symposium. OSHR publicity efforts will increase as the time for the symposium nears, and we will run the press room during the event.

This year the OSHR helped publicize and developed media interest in the first NINCDS-sponsored consensus development conference. The subject of the conference was long-term management of febrile seizures, a topic of special interest to magazines and newspapers reaching families with young children. We are now planning similar public information support for a consensus development conference on Reye's Syndrome, planned for March 1981. In the latter project, we work closely with representatives of several voluntary agencies concerned with this disorder.

Many other regular services to voluntary agencies continued in 1979. These included publication of an annual directory of the agencies, supplying publications for their general distribution, and new mailings of RESEARCH CURRENTS.

Fiscal 1980 saw national distribution of NINCDS's public service announcements on detection of hearing loss in young children. These spots were developed with the assistance of the NIH Audiovisual Branch. There were four spots: a 30-second spot for television, and 60-second, 30-second, and 10-second spots for radio. Early in January 1980, these spots were sent to every commercial TV and radio station in the U.S.--some 6,700 outlets. The recipients were asked to return cards indicating how often they planned to use the spots. Within one month, some 3,700 showings had been promised, an estimate the Audiovisual Branch believes to be conservative since less than 200 stations returned cards. The Branch also reported that when the television spot was market-tested by the Health Message Testing Service (HMTS), audience response was significantly higher than the HMTS average for attention and recall of the main idea, and better than any other message tested to date. According to the HMTS report, the NINCDS "Hearing Loss" TV spot "did a good job in communicating its copy points....The message was seen to be aimed at parents and women, and the instructions for the hearing test were considered to be easily understood."

On August 15, 1980, the NINCDS observed its 30th anniversary. To publicize this milestone, the OSHR issued a personal services contract for a photographer to give us several dozen color photographs of NINCDS scientists and administrators at work. The photographs will be used in the new Institute brochure now being designed, and have proven popular with reporters doing stories about the Institute's first 30 years. A four-page centerfold anniversary story, using many of the new photographs, appeared in the August 19 issue of the NIH RECORD. The Institute director gave "30th anniversary" interviews to reporters from the Journal of the American Medical Association, Medical Tribune, U.S. Medicine, Chemical and Engineering News, and a radio science program, "Man and Molecules." Also, a logo designed to honor the anniversary appeared in many NINCDS publications issued throughout the anniversary year.

Brain research will receive international exposure when an ambitious eight-part series on the topic is completed by Channel WNET-13, part of the public broadcastin system. The programs will be aired in Britain and Germany, as well as the United States. The Office of Scientific and Health Reports has arranged interviews with NINCDS scientists to provide the producers with background information and this year NINCDS awarded $200,000 to WNET-13 in support of the project. The funds were awarded through the National Science Foundation. We are looking forward to working closely with the producers as the series goes into production in the next year.

The stature of the OSHR staff was enhanced this year with the arrival of a gifted and highly respected science writer, Joan Steen Wilentz, to serve as expert consultant in the Publications Section. She has overseen the awarding of two personal services contracts with freelance writers for new Hope Through Research pamphlets on spinal cord injury and stuttering.

The OSHR continues to be respected for its talented staff and the quality of training it can provide. This year one staff member was eagerly sought by another NIH office before electing to remain with OSHR in the newly created position of deputy chief. A second staff member was plucked from the ranks of OSHR to become chief of public information for the National Institute of General Medical Sciences. And a third writer-editor advanced within the office from GS-7 to GS-9.

This year, the OSHR helped train one STRIDE employee in public relations. We are working with a well-known Black public relations expert to identify promising minority science writers and public relations students who would benefit from a tour with this office.

In addition to this special effort to provide employment opportunities for minority students, OSHR supported the Institute's EEO effort by developing, editing, or writing a variety of publications aimed at attracting new minority talent to the Institute. Also, this year a Spanish-speaking TV producer from San Antonio was appointed to the Science Information Program Advisory Committee; she has already been helpful in advising us on ways to reach the Spanish-speaking community.

Scientific Publications Section

The Scientific Publications Section produces and distributes publications for the general public and for a variety of scientific and professional audiences. The Section serves various administrative units of the Institute, ad hoc committees preparing reports, and outside organizations in the neurological and communicative disorders fields. The services include planning, clearance, writing and editing of publications; securing design, layout and printing; distributing and storing publications; and subsequent revision and reprinting according to demand. The Section works with the NIH Printing Unit, the Medical Arts and Photography Branch, and the Government Printing Office in producing publications, and also serves as the Institute's supply center for these materials.

The Institute's Monograph Series continues, with 23 titles to date, 12 of which are in print. Two new monographs published in fiscal 1980, The Neurological Bases of Language Disorders in Children: Methods and Directions for Research and Workshop on the Neurological Basis of Autism, were widely distributed.

A good beginning was made toward revising, updating and expanding the Institute's Hope Through Research pamphlet series. These pamphlets continue to be very popular with the general public. They provide information of interest and value to patients and their families, and describe research approaches to the various neurological and communicative disorders. New pamphlets on Huntington's disease and on aphasia were published and widely distributed, and at the close of the fiscal year new pamphlets on cerebral palsy and on spinal cord injury were in press. New pamphlets on the dementias and on stuttering were nearing completion, and revisions of pamphlets on epilepsy and on Parkinson's disease were under way. An expert consultant writer-editor devotes full time to the task of strengthening this series, and is giving special attention to the needs of Blacks and Hispanic communities for health information in the neurological and communicative fields.

NINCDS fact sheets are another series of publications the Section has developed to meet a pressing need for information about lesser known neurological and communicative disorders. Now in print are 12 fact sheets, two new titles having been added in the past year: Neurofibromatosis and Tourette Syndrome. A revised fact sheet on narcolepsy is in press. Four other titles are undergoing revision or reprinting: Friedreich's Ataxia, Torsion Dystonia, Diabetic Neuropathy, and Autism. A Spanish language version of the Autism fact sheet is being published--the Institute's first foray into Spanish language pamphlets in almost 10 years.

A series of guides for professional health practitioners was begun in 1978 with Diabetic Neuropathy--A Scientific Guide. A second in this series, on Alzheimer's disease, is being written under contract. Plaudits given the diabetic neuropathy booklet revealed a need for more short, down-to-earth, clearly written literature for nurses and other paramedical personnel on relatively uncommon neurological disorders, and the Section plans to expand this series as time and resources permit.

Another series of pamphlets, produced annually by the Section, are the special reports to Congress. Summaries of the latest research in the various disorder areas, these reports are written by the entire OSHR writing staff for the annual appropriations hearings, and then produced as leaflets for public information use throughout the year. The special reports are increasingly being used by voluntary agencies seeking to keep their local chapters posted on research developments. This year the reports were published in a new, more attractive two-column format, with more use of color. Nine reports were published:

- Amyotrophic Lateral Sclerosis
- Epilepsy
- Huntington's Disease
- Multiple Sclerosis
- Muscular Dystrophy and Other Neuromuscular Disorders
- Parkinson's Disease
- Spina Bifida and Neural Tube Defects
- Spinal Cord Injury and Nervous System Trauma
- Stroke

NINCDS's Office of Biometry and Field Studies has embarked on a long-term program of hospital studies to produce authoritative statistics on incidence, prevalence, and costs of the major neurological and communicative disorders. A by-product of this program will be a series of short, popular format booklets presenting the distilled results of the studies. The first in this series, a National Survey of Stroke, was produced by the Section from raw materials submitted by the Office of Biometry and Field Studies, and a second, on head and spinal cord injury, was in process of production at the close of the fiscal year.

Two periodical issuances, not publications but essential to the OSHR's mission, are NINCDS Notes, a monthly Institute news item service to journal editors, and Research Currents, a triannual packet of lay audience science articles and other materials for some 55 voluntary agencies sharing interests with NINCDS. Research Currents was begun in Fiscal 1979, and has met with a highly favorable response.

An NINCDS Fact Book, providing historic, geographic, and fiscal information about the NINCDS program in an attractive, colorful format, was published. This will be an annual publication.

A full-color, profusely illustrated NINCDS brochure describing the Institute was prepared by the Section and sent to the Government Printing Office.

A variety of miscellaneous pamphlets and documents were produced, including eight pamphlets offering MEDLARS search strategies for neuroscientists, three directories, and a booklet containing a series of newspaper articles on brain research. Also published were a pamphlet on using MEDLINE for literature retrieval in the communicative sciences, a pamphlet on NINCDS minority biomedical programs, and a guide to extramural NINCDS programs.

The Section lent substantial assistance in the continuing distribution of various technical reports published in the past several years, including reports of the Epilepsy and Huntington's Disease Commissions, the Institute's National Research Strategy Reports, and a Central Nervous System Trauma report.

Public Inquiries Section

Responsibility for handling correspondence and telephone inquiries about NINCDS research, programs, and policies is centered in the Public Inquiries Section. Information specialists assigned to the section answer questions on more than 600 neurological and sensory disorders, coordinating replies as necessary with the Office of the Director, intramural scientists and grantees, and the NIH and HHS Secretariat.

Inquiries from patients with neurological and sensory disorders and their families concern research and all other aspects of a specific illness. In order to answer their questions on rehabilitation, patient care, health services, and financial assistance, staff members must obtain specific information from other components of HHS, other Government agencies, and state agencies through which services and financial aid are channeled.

Last year 580 individually prepared responses were sent to the Institute's lay and medical audiences. Another 182 responses to controlled letters from the Congress and the White House were written and coordinated with the NIH Secretariat. Many other inquiries were answered with printed materials. In all, NINCDS responded to requests for 253,075 publications, including 116,680 Hope Through Research pamphlets, 61,165 fact sheets, 2,521 monographs, and 72,709 miscellaneous publications.

Public Inquiries Section personnel plan and develop the NINCDS annual Exhibits Program, and act as Institute spokespersons at the medical and scientific meetings to which the various exhibits are sent. Last year, a new portable exhibit was developed to interest minorities in scientific careers, and the exhibit schedule was doubled over the previous year to include meetings of the National Medical Association in Dallas, the Biomedical Minority Support Symposium in Atlanta, the Career Planning and Job Fair in San Diego, and the National Coalition of Spanish Speaking Mental Health Organizations in Washington, D.C. OSHR and EEO personnel alternated as Institute spokespersons at these meetings.

A relatively new effort by the Institute to acquaint primary physicians with advances in clinical neurology through its Exhibits Program continued last year at meetings of the American Academy of Family Physicians in Atlanta, and the American Academy of Pediatricians in San Francisco.

Last year, exhibits also were sent to meetings of direct professional interest to the NINCDS: the American Academy of Neurology in St. Louis, the American Academy of Otolaryngology in Dallas, the Society for Neuroscience and the American Speech and Hearing Association, both in Atlanta.

Employee information activities have grown rapidly in the past year. Staff in off-campus locations have become increasingly better informed of Institute activities through NINCDS Clips, a selective reprint of newspaper stories and magazine articles about NINCDS research, programs, and personalities. Eleven issues of NINCDS Clips were published and distributed to Branch and Laboratory Chiefs for posting within their work areas. The NINCDS Clips also were distributed to voluntary health agencies and to NINCDS Council members.

The employee information program was strengthened further by more effective use of the NIH Record reporting Institute research and personnel changes. In all, 8 news stories and 6 feature stories--some of which were picked up by other publications for further distribution--were prepared by a writer in this Section.

The Public Inquiries Section provides materials for the Institute's Advisory Council meetings, updates the Council Directory, and plans the annual Council dinner. The head of the Section also serves as information liaison with the Extramural Activities Program and with the Program Directors in the Federal

Building; she is responsible for identifying grantee research appropriate for use in Institute reports and publications, and writes annual special reports for Congress on cerebral palsy and spinal cord injury.

The head of the Section also serves as the Institute's Freedom of Information Coordinator. This year the Section responded to 35 requests for summary minutes of the meetings and to 120 requests for substantive information about the Institute's programs, including a time-consuming request from a Chicago attorney who personally reviewed, and later requested copies of all NINCDS and NIH files pertaining to chiropractic.

Although not a separate section, the Media Liaison effort, directed by the OSHR deputy chief responds to inquiries from representatives of the news media, issues news, supports special events, and develops media interest in the broad range of activities carried out by NINCDS.

In the initiative's second year of operation, local and national coverage of NINCDS activities included appearances in print, radio, and television. In several instances, wire service stories and locally produced television footage was nationally syndicated, achieving greater exposure for the Institute.

Three major stories in THE NEW YORK TIMES spotlighted the work of NINCDS and its grantees: a page 1 story on the dangers of sexual relations in pregnancy featured a grantee's work on data produced by the Collaborative Perinatal Project; another article explained the freeze-fracture and slam-freezing techniques used at NINCDS; and an interview with an NINCDS otolaryngologist provided an article on motion sickness and vestibular mechanism research.

A suggestion from the OSHR deputy chief to a TIME magazine correspondent resulted in an eight-page cover story on back pain that featured comments from the Deputy Director, NINCDS. Interest also continues in stories about brain and nervous system research, and with the proliferation of new science magazines, OSHR is increasingly turned to as an information resource.

The release of hostage Richard Queen after he was stricken with multiple sclerosis generated a flurry of press inquiries to the OSHR. Reporters were unprepared for the situation, and sought basic background on the disorder. The deputy chief provided this information and in several instances arranged access to an NINCDS scientist.

OSHR is occasionally asked to provide swift access to the press when considered appropriate. An example of this prompt cooperation occurred when the NINCDS Director wanted to alert physicians and the public to the need for increased vigilance in a peak period of Reye's Syndrome incidence. Both wire services responded with stories within hours, as did Physicians' Radio Network.

Emphasis continues on developing and maintaining good rapport with editors and writers. The OSHR deputy chief visits writers with major publications who are newly assigned to the Washington area so that the reporters can begin their work in Washington with an understanding of NINCDS and its research.

Topics suitable for radio coverage in the NIH RADIO TIPS series are suggested throughout the year to the NIH Audiovisual Branch. NINCDS scientists provide excellent cooperation with this series and other publicity-related efforts. The Section head keeps in touch with laboratory and branch chiefs to remain aware of progress in NINCDS research. Future plans include an effort to learn more about extramural research.

ANNUAL REPORT
October 1, 1979 through September 30, 1980

Office of Program Planning and Evaluation
Office of the Chief

National Institute of Neurological and Communicative Disorders and Stroke

Fiscal year 1980 has been a year of change and adjustment for OPPE. In August, 1979, Dr. George Murray resigned as Director after spending much of his time during the previous two years on the primary operational responsibility for the coordination and publication of the "National Research Strategy for Neurological and Communicative Disorders". This document consists of an Executive Summary and ten volumes summarizing the findings and recommendations of seven categorical expert panels and articulates the research goals of the Institute for the next decade. Dr. O. Malcolm Ray, formerly Deputy Director of the Extramural Activities Program, was asked to serve as Chief of OPPE for an interim period during which the Institute wished to make an in-depth review of its structure and the activities for which it should be responsible.

As often occurs under these circumstances, there have been a number of other staff changes. Because of some de-emphasis on the Institute's informational activities, Mr. Alfred Weissberg was permanently assigned to the Fundamental Neurosciences Program. Ms. Irene Ludwin, a technical assistant who had been with the Institute for more than 20 years resigned due to poor health. Mr. David Smith, a computer specialist and Mr. Michael Ermel, a computer programmer accepted positions elsewhere. There has been a complete turnover in the secretarial staff of three persons. Despite severe restrictions on recruiting, all of these vacancies have been filled with Ms. Thelma Martin as program analyst, Mr. Lawrence Greene (terminated 9/19/80) as computer programmer and Mr. Charles Rice as systems analyst. A medical officer, M. Gilda Marques, who is currently on staff, was recruited in FY 1979.

The OPPE advises the Institute Director and the OD staff on program development, analysis, evaluation and the development of strategic and implementation plans within available resources. It provides staff support to facilitate the integration of the program planning, analysis and evaluation efforts in the categorial program areas and provides the Director and the Executive Staff with assistance in coordinating the development of research plans for meeting these goals.

The OPPE continued the development of an integrated Program Information System (PINS) for the Institute. This will combine programmatic, fiscal and management data into an Institute-wide data base. With extensive input by contractors and some expansion of the Institute's computer and programming capabilities, this is expected to move the Institute's data management resources into the modern era of information technology.

As a legislative focus for the Institute, the OPPE continued to work with appropriate staff of OD/NIH to keep in touch with and to monitor legislative developments in order to safeguard and maintain all elements of the Institute's mission.

During the past year a formal Table of Organization was devised and offically approved. The OPPE now consists of the Office of the Chief, with a Deputy Chief, and two Sections, an Analysis and Reports Section and an Information Technology Section. The activities of these two Sections are summarized below:

Analysis and Reports Section

The Section staff prepared and coordinated the development of the Research and Legislative Plan of the Institute which is concerned with setting major themes, thrusts and tone for the discussion of budgetary requirements for the future years. Input was also solicited and obtained from the Program Directors and from the Director and Deputy Director of NINCDS. Budgetary projections were developed by the Budget Office in close collaboration with the Section. The questions raised by NIH-OD were responded to jointly by the Budget Office and the Section.

The Section prepared and coordinated the annual Evaluation Plan for the research programs of the Institute and developed proposals for the recurrent assessment of the effectiveness of its research programs. The Institute has 3 approved evaluation projects which are to be funded by 1% set aside evaluation funds. Two of these projects lie within CDP and one in IRP. In addition, in response to ASPE demand, for the first time a long range evaluation plan has been developed for assessing the performance of NINCDS research programs. Section staff also served as Evaluation Contact and Institute representative in all activities related to evaluation. The Section provided NIH all the material requested by ASPE regarding the status of ongoing evaluation projects and utilization of their findings and resulting impact.

The Section staff developed, in collaboration with Program Managers and Directors, the Institute responses on a number of issues, and on review and analysis of specific aspects of research programs. It served as the Institute representative at a number of trans-NIH and inter-agency coordinating committees, e.g. Diabetes, Arthritis, Digestive Diseases, Nutrition, etc. It also served in a liaison capacity for reporting research on various subjects, e.g., prevention, toxicology, environmental health, technology transfer, etc. to other agencies, to NIH Institutes and offices and as Clinical Trials Coordinator for NINCDS. In addition, the Section responded to a number of ad hoc queries from a variety of private and public sources regarding NINCDS research as it relates to NHLBI, NIEHS, pain research and research on the handicapped, etc.

Prevention analyses involved identification of the total NINCDS research matrix to extract FY '79 projects related to primary prevention and to one or more of 15 DHHS Prevention Initiatives for the booklet entitled "Healthy People" and for a publication called "1999 Objectives for the Nation". Technology transfer activities required preparation of reports on NINCDS-related technology assessments, on technology Consensus Conferences - Febrile Seizures, Reye's Syndrome and CT Scan, including definitive listings and monitoring of NINCDS emerging technologies for OMAR.

The Section coordinated the development of the annual Implementation Plan of the Institute. This was focused at setting funding priorities within the context of program objectives, research opportunities and available resources. It was done in close collaboration with the Executive Officer and the Budget Officer to assure that their needs are met. In this process, the Section also developed the projections for new and renewal research grant applications to support the resource allocation decisions.

The Section also had the responsibility of coordinating development of the Institute Annual Report. The Section representative worked with the contact persons in all Program Areas and provided them the technical assistance to assure uniformity of format and editorial quality of the Report. The Annual Report is a standard formal Institute document that presents an overview picture of the total scope of NINCDS research as to science, program and budget. Further, it includes detailed information on Intramural Research, in particular, and as such has become to CRISP (NIH Computer Retrieval of Information on Scientific Projects) the sole annual source of Information thereof.

Special Projects

The six research projects of Z. A. Shakhashiri, M.D. described in previous Annual Reports are as follows:

1. Study of Mental Retardation - a retrospective study to discover etiological associations with selected prenatal variables. A manuscript is undergoing revision based on the utilization of more sophisticated statistical methodology in control groups.

2. Public Health Implication Study - to compare perinatal death rates of participants in the collaborative study with death rates of populations in the same cities. There has been no further progress in this study.

3. Normal vs Caesarean Delivery - to compare the outcome of normal delivery with elective Caesarean delivery. The multivariant analysis of the data is underway.

4. Health Status of Populations - to compare the incidence and prevalence of selected disorders in ethnic groups in the U. S. with similar ethnic groups in other countries. The concept is being explored with experts and consultants to determine whether the National Center for Health Services Research (NCHSR) or the Fogarty International Center (FIC) are interested in this approach.

5. Systems of Medical Practice - to compare French and American medical practice in Lebanon. The status is the same as for #4 above.

6. Research on Administration (with NICHD) - to test the hypothesis that authority and responsibility in any bureaucratic hierarchy are equal only in middle levels and that authority disproportionately increases the higher the level. A draft document entitled "Concept of Authority, Should It Be Re-examined?" is under informal review.

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Information Technology Section

The Information Technology Section (ITS) is responsible for developing and maintaining administrative and program information systems for the Institute. The principal project under development is the Program Information System (PINS) which will combine programmatic, fiscal and management data into an integrated Institute-wide data base. The ITS was supported in this effort by two contractors: Pinkerton Computer Consultants for the development of computer programs to fulfill the management requirements, and JRB Associates, Inc. to provide technical support to the Institute and to validate the programs developed by the programming contractor. Major activities of these contractors are reported in the contract narrative.

An integral part of the PINS is an expanded classification system. This Section provided the development and coordination with the scientific staff of the new multi-axis taxonomy.

Other activities of the Section include the design and development of an interactive system for the storage and retrieval of drug reaction data for inpatients as well as outpatients participating in clinical trials. Inpatient data is extracted from the Clinical Center's patient data file and outpatient data and all patients' reaction data can be entered into the system from computer terminals. The system is in the final stage of development prior to release to the Intramural staff. Several other projects were undertaken such as the development of an annual updating system to record special codes assigned to Institute grants, contracts and Intramural projects - BAD, SATT, Prevention, etc. In addition the section provided data base Administrator and maintenance support for the Intramural Management Information System.

The ITS also provides technical support for specific ADP applications in other areas of the institute and coordination of several NINCDS-wide activities. Included in this category are:

- Development procedures, including check lists, for the prepa ration of the quarterly update to the PHS ADP Inventory Data Base and for the preparation of the annual ADP Financial Plan submitted to DCRT. These procedures were used during actual updates making the function of the NINCDS ADP Coordinator more clearly defined and improving the turnaround time for both of the required submissions.

- Initiation of activities related to the assignment to this Section of the responsibility for NINCDS ADP System Security. This function impacts not only on the PINS but also on every ADP resource in the Institute. The initial activities are being focused on the development of an up-to-date inventory of all NINCDS ADP resources. This includes terminals, remote facilities, mini-computers, software systems/programs, personnel associated with NINCDS ADP systems, and ancillary equipment.

Future activities of the Section will be directed primarily to:

- Install the PINS system in modular fashion, training Institute personnel and providing data base Administrator support for the system.
- Maintain existing systems, providing enhancements as required.
- Coordinate ADP reporting for NINCDS to the PHS Inventory, the ADP Financial Plan, and the ADP Systems Security Plan.
- Provide technical assistance for the administrative and management data processing needs of the Institute.

CONTRACT NARRATIVE
Office of Program Planning and Evaluation, NINCDS
Fiscal Year 1980

NINCDS PROGRAM INFORMATION SYSTEM (PINS) N01-NS-8-2301), JRB Associates, Inc., 8400 Westpark Drive, McLean, Virginia 22101.

Title: Validation and Technical Support-NINCDS Program Information System

Contractor's Project Director: Jacqueline Sanders

Allocation: $24,900

Objectives: The contractor is to: 1) provide technical support to the Institute by coordinating the definition, initialization and creation of the data base; 2) assist in the selection and placement of peripheral hardware throughout the Institute; 3) assist the Office in establishing procedures to ensure the efficient and secure operation of the System upon installation; 4) sequentially validate the PINS data and computer programs as they are released by the programming contractor; 5) review validated products with the appropriate members of the NINCDS staff; and 6) train Institute staff in the use of the system, type of output available and the interpretation of various report formats.

Major Findings: JRB developed and presented several sessions of orientation to the PINS project for the programming contractor staff as well as members of the Institute EAP/ODAR and OPPE/ITS. The contractor has been interacting with the programming contractor's staff on specifications presentation, clarification and logic walk-through reviews. Validation of the first module's programs is underway with resultant recommendations for correction and/or improvement. The contractor collected and converted hard-copy data into machine-readable form for purposes of testing programs and establishing necessary tables. Additional data already in machine-readable form was identified and has been provided to the programming contractor. Coordination meetings between the IMPAC system's manager and staff resulted in finalization of specifications for receiving data from and sending data to the IMPAC system. PINS specifications were updated as a result of technical improvements recommended by both the programming contractor and JRB and more current process flows in the Institute.

Significance to the Program of the Institute: The scientific, budget and program information of the Institute is increasing in quantity and complexity. Rapid access to pertinent facts in a timely manner is essential for effective management. PINS is being developed as a data base management system providing on-line access to the data by organizational units throughout the Institute. Data will be accessible when and where it is needed and in a form that can readily be used. PINS will maintain data currency, validity and compatibility between it and existing NIH systems such as IMPAC, CAS, ARMS and TDCS.

Proposed Course: The contractor will complete validating all programming products for the first data module; provide Institute user training and system and user level documentation. These activities will be similarly performed for the three remaining data categories.

CONTRACT NARRATIVE
Office of Program Planning and Evaluation, NINCDS
Fiscal Year 1980

NINCDS PROGRAM INFORMATION SYSTEM (PINS) (NO1-NS-9-2317), Pinkerton Computer Consultants, Inc., 65 West Street Road, Building C, Warminster, Pennsylvania 18974.

Title: Program Development and Implementation - NINCDS Program Information System

Contractor's Project Director: Dr. Dennis Clague

Allocation: $202,347

Objectives: The contractor is to write, test, install, parallel test and document the computer programs for the NINCDS Program Information System (PINS). The contractor will insure the timely delivery of products which meet the specifications and requirements of the system. Four categories of data will be processed: Project Program Status and Reports (grants, contracts and intramural projects); Operating Expenses, Budget/Program Analysis and Personnel.

Major Findings: The system is being developed in modular fashion. The programs for the first of four units have been coded and are in the test and validation stage.

Significance to the Program of the Institute: The scientific, budget and program information of the Institute is increasing in quantity and complexity Rapid access to pertinent facts in a timely manner is essential for effective management. PINS is being developed as a data base management system providing on-line access to the data by organizational units throughout the Institute. Data will be accessible when and where it is needed and in a form that can readily be used. PINS will maintain data currency, validity and compatibility between it and existing NIH'systems such as IMPAC, CAS, ARMS and TDCS.

Proposed Course: The contractor will complete development of programs for the first unit and the remaining three categories of data along with respective documentation.

ANNUAL REPORT
October 1, 1979 through September 30, 1980
Office of Biometry and Field Studies, OD
National Institute of Neurological and Communicative Disorders and Stroke

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Annual Report
for period October 1, 1979 through September 30, 1980
Office of Biometry and Field Studies
Office of the Director
National Institute of Neurological and Communicative
Disorders and Stroke

The Office of Biometry and Field Studies (OBFS) supports a program in biostatistics, field studies and computer science to further medical research in the areas of neurology and communicative disorders.

The Office is active in a number of specific program areas: Disease-specific computerized clinical data banks, national surveys of disease, and clinical trials, of which the latter are of increasing emphasis.

Intramural Program research collaboration in biometry and mathematical statistics continues to be an important element of OBFS activities, with full-scale collaboration of OBFS investigators in all phases of the projects. The range and variety of problems make full utilization of the varied talents of the OBFS staff which, in addition to expertise in mathematical statistics, include those of physics and computer science. The latter two, for example, are extensively relied upon for the work in computer-aided tomography.

The Office of Biometry & Field Studies is responsible for the National Stroke and Traumatic Coma Data Banks program whose objectives are to provide answers to long-standing research questions and to improve patient management.

During the two years of the current pilot phase of the clinical data bank for stroke (Goals #30, 33, 34), a stroke vocabulary of some 700 variables has been developed and tested, as well as individual centers' data collection forms that will be regarded as part of the patient's medical record. Full-scale data collection has begun and data on 353 patients have been completed and stored in the central computer data bank facility. Six research studies which were proposed by the Principal Investigators are under way.

The pilot data bank centers for traumatic coma (Goals #36, 37, 38, 40, 41) have also developed a vocabulary and data collection forms, which are currently under test with patients at each center. A meeting of neuropsychologists has established a battery of outcome measures for the traumatic coma patients. These members of OBFS are producing a book, Medical Data Bases: Statistical Considerations.

Findings from the national surveys of neurological diseases are being disseminated. A monograph, The National Survey of Stroke (Goal #30), has been submitted for publication as a supplement to Stroke: the Journal of Cerebral Circulation. A brochure for a lay audience on the findings of the Stroke survey has been distributed.

A major report on the results of the Head and Spinal Cord Survey has been accepted for publication as a supplement to the Journal of Neurosurgery.

A report on the findings from the Survey of Intracranial Neoplasms has been submitted to the Journal of Neurosurgery.

Brochures for the latter two reports are in preparation.

A significant effort continues to be focussed on the analysis of data from the Collaborative Perinatal Project. Intensive studies are proceeding in the areas of febrile seizures, neonatal seizures, convulsive disorders in general, cerebral palsy, minimal brain dysfunction and maternal infection during pregnancy. Members of NDP and OBFS have completed the book Minimal Brain Dysfunction: A Prospective Study to be published in the Fall by Lawrence Earlbaum Associates. Other collaborators in NDP and OBFS are at work on two books -- one on the relationship of maternal variables and childhood signs to cerebral palsy, and the other, the association of these variables to seizures in children.

Implementation of a three-stage program is progressing to determine the optimal management of children with febrile seizures. The first stage was the consensus meeting held in May of the year. The purpose of the meeting was to determine the degree to which a policy on management could be stipulated, and to identify areas in need of further research. The consensus statement supported the findings of the Collaborative Perinatal Project in a series of reports by NDP and OBFS. It concluded that the prognosis for children with febrile seizures was excellent, and that there is no evidence that prophylaxis can prevent long-term sequelae. The statement excluded some 60 percent of all children with febrile seizures from consideration for prophylaxis. The statement also delineated several areas of needed research including the determination of safe and efficacious prophylaxis for the small number of children who are at high risk for later epilepsy. The second stage is a survey of current practice and of clinical determinants and rationale for management of children with febrile seizures. This will be used as an element in considering the need for, and potential impact of, further clinical research, as well as providing input for the design of any future clinical trial. A protocol for a clinical trial is under development in collaboration with the Developmental Neurology Branch and the Epilepsy Branch in the event the results of the foregoing stages indicate such a trial is necessary and feasible.

The Survey of Multiple Sclerosis is in the final phase of analysis. A report on the incidence and prevalence of the disease has been submitted to the Annals of Neurology.

Consultation with multiple sclerosis experts will determine the feasibility of a study to examine the validity of physician and hospital diagnosis of multiple sclerosis.

Data collection has been completed in 27 hospitals as part of the feasibility study for the National Hospital Survey of Disease (Goal #30), a survey designed in collaboration with the National Center for Health Statistics (NCHS), which will "piggyback" on the latter's Hospital Discharge Survey.

The first phase of an investigation to determine the feasibility of a major survey of epilepsy (Goal #11) has been successfully completed. The OBFS Advisory Committee unanimously recommended that the second phase, a pilot study, begin as soon as possible.

The processing and tabulation of data have been completed for the community Survey of Neurological Disorders in rural Mississippi, and the analysis of the data and the preparation of reports has begun. This survey is the first to provide comparisons of the prevalence of selected neurological disorders (senile dementia, stroke, Parkinsonism, epilepsy, cerebral palsy, and psychomotor delay) between blacks and whites in a rural setting. Preliminary review suggests that important differences in prevalence of neurological disease between the races will be demonstrated.

An OBFS program to generate descriptive statistics for NINCDS programmatic activities is disseminating the results of studies of data from the NCHS 1979 Hospital Discharge Survey. The "Second Annual Report on Neurological Discharges" was distributed to Program Directors. A report analyzing the prevalence of stroke from data of the 1978 Health Interview Survey has been sent to Stroke: the Journal of Cerebral Circulation. A presentation at an international conference is anticipated for work on the analysis of type-specific mortality due to stroke. This paper will also be submitted to the above-mentioned journal.

Planning for a National Headache Survey (Goals #55, 57, 58) progresses. The objectives are (1) to identify etiological, clinical, and environmental risk factors which may be associated with the occurrence of several major types of headache, (2) to determine the impact of headaches on society by demographic subgroups of the U.S. population; factors such as financial cost, work, productivity loss, and quality of life will be assessed; and (3) to devise a classification system for types of headache which can be used in epidemiologic studies, using the symptomatology and history reported by patients.

OBFS has entered into an interagency agreement with the National Institute of Mental Health to study dementia. The work will be performed by the Johns Hopkins University. The study will generate estimates of the social and economic costs of the disease on medically validated individuals and their families (Goal #17).

OBFS has collaborated with the Experimental Therapeutics Branch on clinical studies of Parkinson disease. Both in-patient and out-patient clinical trials of new drugs or the new application of standard drugs (e.g., lisuride, bromocriptine, lithium) have been initiated with Parkinson patients. OBFS has been involved in the design and analysis of these trials as well as the monitoring of the accumulating data and the analysis of adverse reactions.

OBFS has informally been invited to become the Data Analysis and Data Coordination Center for the proposed Johns Hopkins University clinical trial of Plasmapheresis Treatment for Acute Guillain-Barré. OBFS will accept that responsibility if the project is funded.

OBFS has participated in the design of a clinical trial Study of Efficacy of Spinal Manipulative Therapy on the Performance of Athletes.

A pilot study has been funded by the U.S. Olympic Council on Sports Medicine, Commission on Sports Medicine Modalities. The pilot study may be accomplished at Yale.

The U.S. Olympic Council on Sports Medicine has also funded A Study of the Reliability of Diagnostic Findings Made by Manipulative Therapists. The study, which is in the planning stage, will be accomplished on Olympic athletes at the Olympic Training Center in Colorado Springs, Colorado.

The Departments of Neurosurgery at the University of Virginia and the All-India Institute of Medical Sciences at New Delhi, India, and OBFS are planning a joint Indo-U.S. Study of Head Injury. While important objectives of the proposed study are epidemiologic in nature, relating to the comparisons of the populations at risk in New Delhi and in the Charlottesville, Va., area, the major interest is to examine iatrogenic complications of head injury, such as infection. OBFS will be the Data Analysis and Data Coordination Center.

The Department of State has requested that the U.S. rupee fund be made available for travel of the principal investigators to New Delhi in order to participate in the development of the final proposal.

OBFS is involved in the planning and implementation of a clinical investigation of the prognostic values of CT scanning in low birthweight children, in collaboration with the Developmental Neurology Branch and Children's Hospital of D.C. Data coordination and analysis will be performed by OBFS.

OBFS is also involved in the planning and implementation of a clinical trial on the effect of phenobarbital therapy in children with febrile seizures on their cognitive development. OBFS will act as data coordinating center for this project, and collaborate on the analysis.

NOTE: The following research projects (most recently reported in FY '79) have been completed:

1. Z01 NS 02348-02 -- Simulated CAT Display.
2. Z01 NS 02350-02 -- Statistical Methodology for Medical Data Bases.
3. Z01 NS 02352-02 -- Nearest Neighbor Algorithms for High Dimensional Spaces.
4. Z01 NS 02416-01 -- Gantry Motion Study for a Positron Scanner.
5. Z01 NS 02419-01 -- Cost Considerations in the Generation of Large Correlation Matrices.
6. Z01 NS 02422-01 -- Aliasing Errors in Computed Tomography.

OFFICE OF BIOMETRY AND FIELD STUDIES

Bibliography

Anderson, D.W., Kish, L. and Cornell, R.G.: On stratification grouping, and matching. *Scandinavian Journal of Statistics* 7: 61-66, 1980.

Brooks, R.A., Glover, G.H., Talbert, A.J., Eisner, R.L., DiBianca, F.: "Aliasing: a source of streaks in computed tomograms." *J. Computer Assisted Tomography*, Vol. 3, 1979, 511-518.

Dambrosia, J.M. and Ellenberg, J.H., "Statistical Considerations for a Medical Data Base." *Biometrics*, June 1980.

Ellenberg, J.H. and Nelson, K.B., "Population based vs. clinical based studies in the assessment of the prognosis of a common childhood disorder," *Journal of the American Medical Association*, April 4, 1980.

Ellenberg, J.H. and Nelson, K.B. "Published Recommendations for the Treatment of Febrile Seizures: Their Efficiency vs. Epilepsy." Presented at the Consensus Meeting on Management of Febrile Seizures, May 1980. To be published.

Feigenson, J.S., Fries, J.F., Kunitz, S., McShane, D. and Greenberg, S.D.: Time-oriented functional profile: Practical applications in a stroke database model. *Arch. Phys. Med. Rehabil.* 60: 512-516, 1979.

Gopinathan, G., Tervainen, H., Dambrosia, J., et al., "Lisuride in the treatment of parkinsonism," accepted by *Neurology*.

Gopinthan, G., Tervainen, H., Dambrosia, J., et al., "Studies on parkinson's disease II: evaluation of lisuride as a therapeutic agent." Presented to The American Academy of Neurology, New Orleans, 1980. To be submitted.

Morgenthaler, D., Brooks, R.A., Talbert, A.J., "Noise factor of polychromatic x-ray beam in computed tomography," *Journal of Physical Medical Biology*, Vol. 25, 1980, 251-259.

Nelson, K.B. and Ellenberg, J.H., "Seizure Disorders in Early Childhood as Observed in a Prospectively Defined Population." Presented at International Child Neurology Association meeting, November 1979; to be submitted for publication.

Nelson, K.B. and Ellenberg, J.H., "What Are Nonepileptic Seizures," Letter to the Editor, *Pediatrics* (65), March 1980.

Nelson, K.B. and Ellenberg, J.H., "Natural Course of Febrile Seizures," Letter to the Editor, *Pediatrics* (65), March 1980.

Nelson, K.B. and Ellenberg, J.H., "The role of recurrences in determining the outcome in children with febrile seizures." Presented at the Consensus Meeting on Management of Febrile Seizures, May 1980. To be published.

Nelson, K.B. and Ellenberg, J.H., "Apgar scores as predictors of chronic neurologic disability." Presented to the Child Neurology Society, October 1979. Submitted for publication.

Nelson, K.B. and Ellenberg, J.H., "They Don't Do Very Well," Letter to the Editor, Pediatrics (65), March 1980.

Sever, J.L. and Ellenberg, J.H., et al., "Toxoplasmosis: Maternal and Pediatric Findings in 23,000 Pregnancies." Presented at the Infectious Disease Society for Obstetrics and Gynecology, May 1980. Submitted for publication.

Stuart, W., Gopinathan, G., Tervainen, H., Dambrosia, J., et al., "Studies on parkinson's disease I: tests of motor function." Presented to The American Academy of Neurology, New Orleans, 1980. To be submitted.

Talbert, A.J., Brooks, R.A., Morgenthaler, D., "Optimum energies in dual energy computed tomography." Journal of Physical Medical Biology, Vol. 25, 1980, 261-269.

Tervainen, H., Gopinthan, G., Dambrosia, J., et al., "Tetrahydrobiopterin in normal aging." Submitted to Journal of Neurology, Neurosurgery, and Psychiatry.

OFFICE OF BIOMETRY AND FIELD STUDIES
Section on Mathematical Statistics

Consultation with IRP

Dr. Yaar, Neuromuscular Section, Medical Neurology Branch: The effect of L-Dopa on EMG (electromyogram) measurements in human subjects

Dr. Isabel Shekarchi, Infectious Diseases Branch: Determination of Rubella Antibody Levels using ELISA

Sue Pollard and Dr. T. Chase, Intramural Research Program: Parkinson Patients on Guam

Dr. Richard J. Benfante, Laboratory of Central Nervous System Studies: Genetic Markers in Infection with Several Arboviruses

Drs. Calne and Gopinathan, Experimental Therapeutics Branch: Treatment of Parkinson Patients with Lithium for Control of Dyskinesia

Drs. Calne and Gopinathan, Experimental Therapeutics Branch, LISURIDE Treatment of Parkinson Patients

Drs. Calne and Gopinathan, Experimental Therapeutics Branch, Tetrahydrobiopterine Levels in Parkinson Patients

Dr. Teravainen, Experimental Therapeutics Branch, Tetrahydrobiopterine Levels in Normal Aging

Dr. Paul Fedio, Clinical Neuroscience Branch, BH4-levels and Psychometric Function

Dr. John Barringer, Developmental and Metabolic Neurology Branch, Sample Size Determination for Detecting Differences Between Biopsy Methods for GLI and PE

Dr. David Asher, Laboratory of Central Nervous Systems Studies, Comparability of Cell Cultures: A case-control study of copped cell for scrapie

Dr. Amos Palmer, Infectous Disease Branch, Allometry for Four Primate Species

Dr. Christopher Ward, Experimental Therapeutics Branch, Study of Parkinson's Disease in Twins

Dr. Rodney Brooks, Neuroradiology and Computed Tomography Section; Surgical Neurology Branch, Enhancement of CAT and PETT scanning techniques

Dr. John Sever, Infectious Disease Branch, Toxoplasmosis: Maternal and Pediatric Findings in 23,000 Pregnancies

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1980

1. Univ. of Texas-Galveston	(N01-NS-9-2308)
2. Univ. of Cal. in La Jolla	(N01-NS-9-2309)
3. Medical College of VA	(N01-NS-9-2307)
4. Univ. of VA	(N01-NS-9-2306)

Title: Pilot Data Bank Network in Traumatic Coma

Contractors' Principal Investigators:

1. Dr. Howard Eisenberg
2. Dr. Lawrence Marshall
3. Dr. James D. Miller
4. Dr. John Jane

Current Annual Level FY 80		
	1.	$ 99,787
	2.	116,638
	3.	123,559
	4.	97,246

Objectives: The primary objective of this project is to develop an interactive data bank network for traumatic coma patients. This data bank will be used for clinical research and patient management.

Major Finding: The investigators meet regularly to discuss the uniform vocabulary and data collection methods. This data bank is refining and utilizing a uniform clinical vocabulary to collect patient data, including symptoms, test results, therapies and outcomes. The Glasgow Coma Scale is part of this vocabulary. Sections of the vocabulary were selected for revision and assigned to each of the investigators. Data is being collected and entered during the pilot phase of this project.

Significance to the NINCDS Program and Biomedical Research: This Traumatic Coma Data Bank is important for several reasons. Longitudinal data on coma victims will be collected at four centers using uniform definitions and procedures. This information will provide a large body of high quality data for clinical research on the factors influencing survival following coma. Secondly, the data bank will serve as an efficient mechanism for collecting, storing, and retrieving the information collected on a single patient and groups of patients. The number of therapies and monitoring devices commonly utilized during the actue phase of managing traumatic coma necessitates a highly organized data handling capacity. The preliminary utility of this data bank network for clinical research and patient management will be demonstrated.

Proposed Course of the Project: This is a three-year collaborative pilot project involving four centers which collect patient data, a database management center, and OBFS staff which provides some systems support and have the responsibility for data analysis. During the first stage of its operation the effort was focused on refining the uniform vocabulary and developing data collection methods. The second stage is a test phase when this vocabulary and procedures for collection, entry and retrieval are implemented on a trial basis. Later stages will involve final revision of vocabulary and methods, implementation and analysis.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1980

1. Univ. of Maryland (N01-NS-9-2302)

2. Univ. of S. Ala. (N01-NS-8-2397)

3. Duke Univ. (N01-NS-8-2396)

4. Boston Univ. (N01-NS-8-2398)

Title: Pilot Data Bank Network in Stroke

Contractors' Principal Investigators:
1. Dr. Thomas Price
2. Dr. Jay Mohr
3. Dr. Albert Heyman
4. Dr. Philip Wolf

Current Annual Level:
1. $141,000
2. 157,500
3 139,000
4. 127,000

Objectives: The primary objective of this project is to develop a computerized interactive data bank network which will contain uniform, longitudinal data on stroke patients to aid both research and patient management. This is a collaborative project involving four separate medical centers which will collect data, a data base management center to store and manipulate the data, and staff at OBFS who have the responsibility for data analysis.

Major Findings: This project has produced a uniform vocabulary of data to be collected on stroke patients from the collaborating centers. This vocabulary includes demographic background diagnosis, signs, symptoms, test result, medical and surgical therapy, complications, and measures of stroke deficit and recovery. The methods and procedures for data collection and entry into the computerized data bank have been developed and are currently being used at all centers. Retrieval programs are being written now for administrative use.

Significance to the NINCDS Program and Biomedical Research: The Pilot Data Bank Network in Stroke is important for several reasons. First, the data bank network will provide a resource of high quality data on the clinical course of stroke. It is intended that this data be used for research on the factors influencing stroke pronosis, and for other clinical investigations. Secondly, the interactive data bank provides the physician with efficient data collection and timely access to patient data. Also projected is the provision of prognostic data from subgroups of similar patients. This is a pilot project, and is intended to serve as a prototype for a national databank network for neurological disorders.

Proposed Course of the Project: The Pilot Stroke Data Bank Network has completed a test phase (90 days) during which the uniform vocabulary, patient ascertainment procedures and data collection methods were being implemented on a trial basis. The data collected during this period were extensively examined for errors. The Pilot Stroke Data Bank Network is in the second year of its pilot phase. Data is being collected, examined for errors, and added to each data base. Data collection and entry procedures are being revised as need dictates. Any necessary revisions in methods or vocabulary will be made prior to the initiation of the actual data bank.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1980

Stanford Univ. (N01-NS-8-2390)

Title: Data Bank Maintenance Center for Pilot Data Bank Network Projects in Stroke and Traumatic Coma.

Contractor's Project Director: Dr. James F. Fries

Current Annual Level: $202,453.

Objectives: TOD-ARAMIS is the Data Bank Maintenance Contractor for the Pilot Projects to establish Data Bank Networks for Stroke and Traumatic Coma. During the three and a half year contract perod ARAMIS will provide the computer interface for these projects, which includes data entry, storage, and retrieval, utilizing the Time-Oriented Data Base (TOD) system. Data will be collected at pilot centers and entered into separately maintained Stroke and Coma data banks available for retrieval within and among the pilot centers.

Major Findings: TOD-ARAMIS has created the computer Schema for the Stroke Data Bank uniform vocabulary and developed methods for entering the Stroke data into the central data bank. The Schema is a dictionary of data elements contained in the patient chart. Data entry personnel at the four stroke centers have been trained and several retrieval programs have been developed.

Significance to the NINCDS Program and Biomedical Research: The TOD-ARAMIS Data Bank Maintenance Center is crucial to the success of the eight data banks which comprise the Pilot Data Bank Networks for Stroke and Traumatic Coma. TOD-ARAMIS serves as the central data repository, maintains data integrity and provides programming, education, and systems support to the eight centers. The availability of this database computer software has made these data bank networks feasible without extensive investment in new programming activity; applying this system to stroke and traumatic coma is a first step in the development of an optimal system for a national data bank network for neurological disorders.

Proposed Course of Project: The Stroke schema is complete and the present focus is on data entry during the current test phase of the Pilot Stroke Data Bank Network. By the early part of FY 1980 the test phase ended and the Maintenance Center is now focusing its activities on storage and retrieval for Stroke. The Coma data bank contractors are finalizing their vocabulary and the coma schema has been constructed to reflect the current vocabulary. Data is being entered at each center and analyzed for errors.

CONTRACT NARRATIVE
Office of Biometry & Field Studies, OD, NINCDS
Fiscal Year 1980

ARTHUR YOUNG & CO. (N01-NS-0-2326)

Title: Assessment of Data Bank Methodology

Contractor's Project Director: Dr. Craig Cook

Current Annual Level: $110,329.00

Objectives: The main purposes of this contract are to assess the effectiveness and utility of the present computer system, both hardware and software in use during the pilot phase of both Stroke and Traumatic Coma; and to compare the system to other presently available commercial and institutional systems. The contractor will, if necessary recommend modification or replacement of software and/or hardware with a more suitable system.

Major Findings: Arthur Young & Co. has assessed the data bank environment currently in use by the Stroke and Traumatic Coma projects, by interviewing project team members, management, statistical and programmer analyst personnel, as well as members of the Data bank Network Group at Stanford University. The Company has also interviewed vendors, government agencies and universities with alternative systems and is analyzing and comparing the systems. They're part on the assessment phase is nearing completion.

Significance to the NINCDS Program and Biomedical Research: For most neurologic disorders there's a paucity of data for clinical research on the natural history of disease, on etiology, on the effectiveness of intervention and on methods of prevention. In order to provide longitudinal information, OBFS has undertaken the Stroke and Traumatic Coma Data Base Systems. The pilot projects are utilizing existing computer software in order to concentrate resources on the problems of clinical data collection and to avoid the problems of introducing an unproven system.

If it is demonstrated that data of high quality can be collected in a uniform manner, then NINCDS will consider the expansion of a data bank system to other centers and disease or disorder areas. A computer system must be capable of growing as this project does, to provide human-engineered, efficient, secure data base management. We hope this contract will guide us to such a computer system which also can be applied to patient registries, clinical trials, and other large scale research studies which depend upon rapid and accurate storage and retrieval of longitudinal clinical data.

Proposed Course of the Project: The contractor is about to submit the report ending Phase I, giving recommendations and a model or an alternative set of models for a national data bank network in neurologic disorders. If it is determined to go ahead with Phase II of the project, the contractor will submit a detailed set of recommendations and specifications for a national data bank. Included items covered will be: hardware, software systems, programming considerations, location for maintenance center and operational cost estimates.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1980

WESTAT, INC. (NO1-NS-6-2333)

Title: Nationwide Study of Stroke

Contractor's Project Director: Morton Robins

Current Annual Level: $ 0

Objectives: The primary objective of this survey is to produce national estimates and accompanying measures of precision for the incidence, prevalence, and economic costs of stroke. It would be accomplished by devising and testing a method for carrying out the survey, and for presenting the statistical results of the survey, including the sampling errors.

Major Findings: The field work of the survey and the data analyses have been completed. A clinical algorithm was applied to the abstracted hospital records which classified the records according to type of stroke and degree of confirmation of the diagnosis in the medical records. Analyses have been made relating the clinical data with the type of stroke and selected age-sex groupings. The final report has been received from the contractor. This report has been reviewed and a series of articles containing the clinical, epidemiologic, and economic findings are being written for submission for publication in a professional medical journal or as a supplement to the journal.

Significance to the NINCDS Program and Biomedical Research: This survey is important for two reasons. First, it provides national estimates of the incidence, prevalence, and economic costs of stroke. These estimates are especially useful to NINCDS for purposes of program planning and allocation of funds. Second, the survey will demonstrate to health investigators the value of probability sampling as a tool in sample selection. Probability sampling is the only general method available which can provide a measure of the precision of an estimate. Though this method is widely used in other areas, it is largely neglected in health studies. This survey, and the others of the NINCDS Survey Program, will demonstrate that probability sampling is both desirable and feasible for certain types of health studies.

Proposed Course of the Project: The medical records were abstracted and pertinent information on the patient's demographic characteristics, the diagnostic categorizations of the stroke, date of onset, medical history of previous strokes or TIA's, clinical signs and symptoms, diagnostic findings, treatment, and outcome of hospital care were recorded for each stroke discharge selected in the sample hospitals. In addition, the hospital's business office was asked to furnish data on the direct medical charges to the patient or third-party payer on those cases discharged during 1975. A subgroup of surviving patients (or close relatives) was also interviewed to obtain information on direct expenditures related to the stroke incurred during 1975 by the patient or the family. Additional facts on other aspects of economic impact of a stroke on the patient and the family were collected.

Moreover, for those discharged patients in the sample that were presumed to have had an initial stroke attack, their survival status was determined as of December 31, 1975, in order to calculate prevalence. The data collected in this survey has been analysed and the final report from the contractor has been received. This contract is now completed. The final report has been reviewed and a series of articles containing the clinical, epidemiologic, and economic findings are being written for submission to a professional medical journal. A monograph of the complete study will also be published in fiscal year 1980.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1980

RESEARCH TRIANGLE INSTITUTE (N01-NS-4-2334)

Title: Survey of the Incidence, Prevalence and Costs of Head and Spinal Cord Injury

Contractor's Project Director: Dr. Daniel G. Horvitz

Current Annual Level: No cost to the Government.

Objectives: The chief aim of the NINCDS National Head and Spinal Cord Injury Survey was to develop estimates of incidence, prevalence, and economic costs for the United States population and selected subpopulations. These estimates were based on a sample of cases which have been selected using the techniques of probability sampling. These techniques are generally more expensive to use than other techniques of sampling but they offer the only general approach which permits the determination of levels of precision for the sample estimates. In this NINCDS survey, levels of precision were obtained for the major estimates of interest.

Major Findings: The objectives of this survey have been realized and the findings have been presented to NINCDS in the form of a final report. NINCDS staff have reviewed the contractor's final report and prepared a manuscript on major findings which will be published as a supplement to the Journal of Neurosurgery.

Significance to the NINCDS Program and Biomedical Research: The Head and Spinal Cord Injury Survey of NINCDS will have major impact on Institute programs in two distinct ways. First, the survey was designed as a tool for program planning. It provides an indication of the scope of the head and spinal cord injury problem as well as the economic costs (both direct and indirect costs) of the problem. With this information, and information from surveys of other disorders, program planners are better able to justify their research priorities and needs.

Second, this survey and others sponsored by NINCDS established that national surveys of relatively rare disorders can be feasible in certain instances using a case finding approach. This realization led to the development of a multipurpose survey which encompasses many disorders. The multipurpose survey will be a periodic survey in which estimates pertaining to various points in time (e.g., yearly, every five years) are obtained and analyzed for trends. This multipurpose survey will be major in scope and will have a significant impact on the programs of several NIH Institutes, the National Center for Health Statistics, and the Center for Disease Control.

Proposed Course of the Project: The study is completed and the final report has been submitted. A manuscript that will serve as the principal report on the project is now in press.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1980

RESEARCH TRIANGLE INSTITUTE (263-78-C-0132)

Title: Case Verification and Supplemental HSCI Analyses

Contractor's Project Director: Mr. Paul Moore

Current Annual Level: No cost to the Government.

Objectives: After careful examination of the final report of the Head and Spinal Cord Injury Survey (Contract NO1-NS-4-2334), it became evident that not all needed analyses had been anticipated and carried out prior to the expiration of the contract. The primary objective of this project is to undertake new analyses which will enhance the value of the monograph to be published on major findings from the survey. In addition, the algorithm which has been used in the main survey to determine medical eligibility for cases of spinal cord injury is to be evaluated in a small-scale specificity investigation.

Major Findings: NINCDS has received the new analyses and a report on the validity check.

Significance to the NINCDS Program and Biomedical Research: This project is of critical importance to NINCDS because the findings are needed for the major report on the Head and Spinal Cord Survey which will be published in a prestigious medical journal. The report will likely have a significant impact on the health care providers who have an interest in injuries to the head and spinal cord.

Proposed Course of the Project: All of the objectives of this project have been reached.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1980

WESTAT, INC. (N01-NS-4-2336)

Title: Survey of Intracranial Neoplasms

Contractor's Project Director: Thomas G. McKenna

Current Annual Level: $ 0

Objectives: The primary objective of this survey is to produce national estimates and accompanying measures of precision for the incidence, prevalence, and economic costs of intracranial neoplasms.

Major Findings: The main survey has been completed and the findings have been presented to NINCDS by the contractor in the form of a final report. The report has been reviewed and additional data is being collected from the hospitals and certain analyses are being redone to improve the quality of the findings. The clinical, epidemiologic and economic findings will be presented in articles which will be submitted for publication in a professional medical journal.

Significance to the NINCDS Program and Biomedical Research: This survey is important for two reasons. First, it provides national estimates of the incidence, prevalence, and economic costs of intracranial neoplasms. These estimates are especially useful to NINCDS for purposes of program planning and allocation of funds. Second, the survey will demonstrate to health investigators the value of probability sampling as a tool in sample selection. Probability sampling is the only general method available which can provide a measure of the precision of an estimate. Though this method is widely used in other areas, it is largely neglected in health studies. This survey, and the others of the NINCDS Survey Program, will demonstrate that probability sampling is both desirable and feasible for certain types of health studies.

Proposed Course of the Project: The main study has been completed and the final report was submitted by the contractor. After careful examination of the final report it became evident that certain ICDA categories needed to be examined in order to validate the findings before publication. Some of the participating hospitals have been asked to furnish photocopies of selected patient records and the data will be reanalysed. The contract has been extended in order to complete the study. The clinical, epidemiologic and economic findings will be presented in articles which will be submitted for publication in a professional medical journal.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1980

NATIONAL ANALYSTS, INC. (NO1-NS-4-2335)

Title: Survey of the Incidence, Prevalence, and Costs of Multiple Sclerosis

Contractor's Project Director: Beth Rothschild

Current Annual Level: No cost to government

Objectives: The primary objective of this survey is to produce national estimates and accompanying measures of precision for the incidence, prevalence, and economic costs of multiple sclerosis.

Major Findings: The data are being analyzed and the contractor will report the findings to the Institute..

Significance to the NINCDS Program and Biomedical Research: This survey is important for two reasons. First, it provides national estimates of the incidence, prevalence, and economic costs of multiple sclerosis. These estimates are especially useful to NINCDS for purposes of program planning and allocation of funds. Second, the survey will demonstrate to health investigators the value of probability sampling as a tool in sample selection. Probability sampling is the only general method available which can provide a measure of the precision of an estimate. Though this method is widely used in other areas, it is largely neglected in health studies. This survey, and the others of the NINCDS Survey Program, will demonstrate that probability sampling is both desirable and feasible for certain types of health studies.

Proposed Course of the Project: The contractor will perform various analyses based on all the different types of data collected; prepare a final report; and prepare three journal articles on the results of the study.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1980

UNITED STATES BUREAU OF THE CENSUS (Y01-NS-7-0031)
UNIVERSITY OF MISSISSIPPI (N01-NS-7-2357)

Title: Survey of Major Neurological Disorders in Copiah County, Mississippi

Contractor's Project Director: Mr. Robert W. Mangold (Bureau of the Census); Dr. Armin F. Haerer (University of Mississippi)

Current Annual Level: $85,000 (Bureau of the Census);
$0 (University of Mississippi)

Objectives: The primary objective of the proposal is to establish the prevalence of six major neurological and developmental disorders (cerebrovascular disease, convulsive disorders, cerebral palsy, psychomotor delay, Parkinson's disease, and dementia) in a well-defined population of southern blacks and whites. A secondary objective is to evaluate the sensitivity and specificity of certain screening questions by means of an item analysis at the close of the study. This analysis is needed because effective screening questions will be used in other morbidity surveys (e.g., the Health Interview Survey of NCHS).

Major Findings: The data collection phase has been completed. The data processing phase is ongoing and strategies are being developed for the data analysis.

Significance to the NINCDS Program and Biomedical Research: At present, there are no adequate data on the prevalance of the six disorders of interest among southern blacks and whites in the United States. A number of studies suggest that stroke is more common among the black population. Mortality data and a few morbidity studies suggest that Parkinson's disease is less common among blacks. A biological explanation of this observation is that both melanin and dopamine are involved in the same metabolic pathway. Dopamine-deficiency in the basal ganglia has been found in patients with Parkinson's disease and is the rationale for the treatment of this condition with L-dopa. Blacks have a higher concentration of dopamine in the basal ganglia than whites which could explain a lower frequency of Parkinson's disease. On the other hand, it may be that blacks with this condition do not seek medical care or receive inadequate care. Mortality tabulations, with all of their biases, suggest that blacks have a predominance of epilepsy and cerebral palsy, but this requires confirmation with morbidity data. The magnitude of the dementia problem has not been studied in any United States population and Copiah County will provide some indication as to whether there is a racial and sex differential in the frequency of this group of conditions.

Proposed course of the project: The field operations for the main study were divided into two types of operations. The first was a household screening operation which was conducted by the Bureau of the Census.

Residents of the study area were screened in their homes by means of a questionnaire administered by lay interviewers who were trained and supervised by the Bureau of the Census. The second type of operation was the examination of persons suspected of having one or more of the disorders of interest on the basis of responses given to questions from the screening questionnaire. The University of Mississippi provided senior, board-certified neurologists to accomplish the neurological examinations and to record the medical findings on forms designed especially for this study. After the close of the field operations, the data was sent to the Bureau of the Census for processing. When the data from the study are available, the Project Director and Associate Project Director from the University of Mississippi will assist NINCDS in the data analysis and the preparation of scientific papers based on the findings of the survey.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1980

RESEARCH TRIANGLE INSTITUTE (NO1-NS-8-2383)

Title: Test of Study Design and Pilot Study for a National Survey of Epilepsy

Contractor's Project Director: Dr. Fred Bryan, Jr.

Current Annual Level: $414,570

Objectives: This project was initiated to develop a new casefinding approach for ascertaining the frequency of cases of epilepsy. The previously used methods have serious deficiencies, and this proposal seeks to remedy them. The goal is to use pharmacies which fill prescriptions for anticonvulsive drugs, to lead to the physicians providing care and thus to the epileptics. In a national survey, estimates of the scope of the epilepsy problem could be obtained for the U.S. population by using techniques of probability sampling.

Major Findings: The design test has been conducted by the Contractor and the proposal for the pilot study has been approved by the Project Officer.

Significance to the NINCDS Program and Biomedical Research: Morbidity surveys of relatively rare disorders are difficult to carry out for the U.S. population. One fundamental problem is that adequate numbers of cases for meaningful analyses may not be included in the sample of individuals selected for study due to stringent requirements for sampling a population. With epilepsy, the problem is compounded because of the perceived social stigma associated with having the disorder. The approach being tested in this contract will, if feasible, yield a cost-effective strategy for the sampling of epileptics who take anticonvulsive drugs. Furthermore, the privacy of the persons included in the study will be safeguarded to a great extent. If this strategy proves successful, a national survey of epileptics could be undertaken which would be invaluable to NINCDS and other organizations responsible for the planning of programs for epilepsy.

Proposed Course of the Project: The project is divided into two parts: a design test and a pilot study. The design test is on a very small-scale and its chief purpose is to lead to the development of methodology for data collection from pharmacies and physicians and to aid in the design of the pilot study. It is scheduled to be completed in July, 1980. The pilot study is of a larger scale and its purpose is to resolve methodological issues which are raised by the investigators or are apparent after the design test. In addition, the pilot study will serve as a dry run for the procedures of the main survey. The pilot study will begin in fiscal year 1981.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1980

WESTAT, INC. (N01-NS-7-2379)
NATIONAL CENTER FOR HEALTH STATISTICS (Y01-NS-7-0030)

Title: National Hospital Survey of Disease
(formerly Comprehensive Disease Statistics Survey)

Contractor's Project Director: Westat, Inc. - Dr. Anita Schroeder
NCHS - Dr. Monroe Sirken

Current Annual Level: Contractor - $ 0
NCHS - 27,500

Objectives: The objectives are to test the feasibility of obtaining hospital incidence and prevalence data for cases identified from abstracted hospital records of a number of neurological and other disorders, from a redesigned Hospital Discharge Survey of the NCHS. A key objective of a successful pilot study would be to develop a survey program that would permit the annual collection of data on these disorders in order to develop trends of their incidence and prevalence.

The national sample of short-stay hospitals would provide a stable base for special studies. These studies would include methodological problems such as multiplicity. It would also provide an unbiased sample of patients, for periodic studies of special interest such as costs of illness, degree of disability, duration of illness, etc. Comparability of data collection methods, and protocols from the same sample of short-stay hospitals, would also permit comparison across disease lines.

Major Findings: The study has been designed and the disease algorithms have been prepared. The contractor has prepared detailed protocols for the feasibility study which is being conducted in the spring and summer of 1980 in 30 hospitals. NCHS has been involved in a cooperative effort with NINCDS to plan and design the study and to work on the many methodological and statistical problems in- volved in the survey.

Significance to the NINCDS Program and Biomedical Research: NINCDS has current contracts for surveys of four neurological disorders, and other surveys are underway and in the planning stage. For several reasons there is a need to consider a more comprehensive approach to the collection of disease statistics. First, there is a considerable degree of redundancy in the present approach, both within NINCDS, and, probably, across Institute boundaries. Redundancy leads to higher than necessary costs associated with the collection of disease statistics data. Second, the present approach leads to delays in obtaining current information, since there are a limited number of surveys which can be conducted at any one time. Third, the methods and protocols used by each contractor differ, and this affects the comparability of data across disease lines. Fourth, and perhaps most important, these data provide planning information based on a limited time period, when in fact trend data, obtained on an annual, prospective basis, would better serve the program planning and program evaluation functions.

The development of a comprehensive system for the collection of disease statistics on a wide variety of diseases would be of great value to NINCDS and other NIH Institutes for it would eliminate the four above-mentioned major problems.

This proposal would establish a cooperative and joint relationship between NCHS and NINCDS, and would provide for an NCHS collection of national health statistics of considerable interest to NINCDS, and potentially, to other NIH Institutes. It would, to the extent that incidence and prevalence data can be obtained from records at short-stay hospitals, supplant NINCDS data collection efforts. NINCDS would continue to analyze the data collected to meet its own program planning needs.

Proposed Course of the Project: This project is a joint venture. The contractor will be responsible for only part of the study. The contractor will develop the methodology and protocols for the feasibility study and the pilot study, will provide the field staff, and will conduct the study and process the data. The disease algorithms will be prepared by NINCDS staff with the aid of other participating NIH Institutes. The sampling plan, counting rules for non-duplication of cases, estimation of sampling variances, and coordination with participating hospitals will be conducted by the National Center for Health Statistics, HRA, under a separate interagency agreement.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1980

NATIONAL INSTITUTE OF MENTAL HEALTH (1Y01-0-0004-00)

Title: ECA Dementia Supplement

Contractor's Project Director: William Eton, Ph.D.

Current Annual Level: $150,000.

Objectives: The study will identify a group of demented individuals and through medical exam the type of dementia will be specified. An estimate of the social and economic costs will also be generated.

Significance to the NINCDS Program: As the population of this nation ages the dementias will represent an increasing medical problem. There are currently no reliable data on the cost of these disorders. This information will be needed to assist in future health planning efforts.

Proposed Course of the Project: This project is an add-on to an existing NIMH program of mental health surveys. After an initial screening for cognitive disability the subjects who are disabled will be given a medical examination. A close relative or friend of those with verified dementias will be used to help establish the history of the disease and estimate the social and economic costs to the affected individual and their immediate circle of friends or relatives.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02450-01 OBFS

PERIOD COVERED

October 1, 1979 through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Study of Efficacy of Spinal Manipulative Therapy on the Performance of Athletes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Dr. Murray Goldstein, Deputy Director, NINCDS
Mr. William Weiss, Chief, OBFS, OD, NINCDS
Dr. Peter Jokl, Associate Professor of Orthopaedic Surgery
Yale University, New Haven, Conn.

Other: Dr. James Dambrosia, Math. Stat., OBFS, OD, NINCDS
Mr. Bernard Kroll, Associate Chief, OBFS, OD, NINCDS

COOPERATING UNITS (if any)

Yale University School of Medicine, New Haven, Conn.

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .03	PROFESSIONAL: .02	OTHER: .01

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The Commission on Sports Medicine Modalities, U.S. Olympic Council on Sports Medicine is supporting a pilot study of the Efficacy of Spinal Manipulative Therapy on the Performance of Athletes. The study is a clinical trial to determine whether manipulative therapy will improve the performance of athletes. Dr. Murray Goldstein, Dr. Peter Jokl, Director of Sports Medicine at Yale, and members of the OBFS have developed the pilot study proposal. Current plans are to accomplish the 250 athlete clinical trial at Yale. Planned end points are athletes and coaches subjective measures of performance, and objective tests such as running, treadmill tests, and tests on machines such as the CYBEX.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02342-03 OBFS

PERIOD COVERED
October 1, 1979 through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Association of Multiple Sclerosis with Certain Serological Parameters

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Ta-Chuan Chen, Ph.D., Mathematical Statistician, OBFS, NINCDS

COOPERATING UNITS (if any)

George W. Ellison, M.D., Associate Professor, Reed Neurological Center
UCLA

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.05	0.05	

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to investigate whether different types of multiple sclerosis (as defined by Reed Neurological Center, UCLA) are associated with levels of certain serological measurements such as I_gG, I_gM, measles and EBV titers. Statistical analysis of clinical data indicated that multiple sclerosis patients of different types (relapse, relapse-progressive, progressive) differed significantly from control patients in certain serological parameters.

Further collection and analysis of clinical data from other neurological centers are in progress.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02310-~~03~~ 04 OBFS

PERIOD COVERED
October 1, 1979 through September 30, 1980

TITLE OF PROJECT (80 characters or less)
A Statistical Study of Sensory-Decision-Theory Method in the Measurement of Experimental Pain

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Ta-Chuan Chen, Ph.D., Mathematical Statistician, OBFS, NINCDS

Other: Joseph Yang, M.D., Research Anesthesiologist, Department of Anesthesiology, Columbia, Univ.

Crawford Clark, Ph.D., Research Psychologist, N.Y. Institute of Psychiatry

COOPERATING UNITS (if any)
Department of Anesthesiology, Columbia University

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Office of Biometry and Field Studies

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.15	0.15	

CHECK APPROPRIATE BOX(ES)
☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to study the Sensory-Decision-Theory Method in determining sensory discriminability and response bias in the response of experimental pain. The result of investigation of the parametric approach for the evaluation of pain response components (Clark, 1971) has been reported at the Second World Congress on Pain 1978. The investigation of the nonparametic estimation of the indices of pain response (Pollack 1964, Hodos, 1971, McNicol 1972) and the sampling behavior of these statistical indices has been broadly studied. Further work includes a cooperative study with the researchers of Columbia University Medical School Department of Anesthesiology in conducting an analgesic study to verify the investigative results.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 NS 02404 - 02 OBFS

PERIOD COVERED
October 1, 1979 through September 30, 1980

TITLE OF PROJECT (80 characters or less)
National Headache Survey

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Ta-Chuan Chen, Ph.D., Mathematical Statistician, OBFS, NINCDS

PI: Frederic D. Weinfeld, Ed.D., Chief, Section on Surveys and Demographic Studies, OBFS, NINCDS

COOPERATING UNITS (if any)

Robert Baumann, M.D., Neurologist, University of Kentucky Medical School

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Office of Biometry and Field Studies

SECTION
Office of the Chief, and the Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .8	PROFESSIONAL: .8	OTHER:

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to measure the extent of the problems of chronic, severe and disabling headaches, the impact of headache disorders on society, and the headache population. In addition, it is planned to examine the present usage of health care by the headache population and to identify etiological and environmental factors which may be associated with various types of headache. The survey questionnaire which includes sections on demography, medical information and history, cost, work and financial loss, etc., is currently under development. A validation study of the questionnaire and the algorithm for identification of major types of headaches are also being designed.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02448-01 OBFS

PERIOD COVERED
October 1, 1979 through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Supraorbital Opacity Pulses During Carotid Artery Compression:
A Method For the Detection of Carotid Obstruction

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: William L. Howell, M.D., Chief Cardiologist, Washington Clinic

P.I.: Ta-Chuan Chen, Ph.D., Mathematical Statistician, OBFS, NINCDS

COOPERATING UNITS (if any)

Department of Neurology, Methodist Hospital, Houston, Texas
Department of Vascular Surgery, Walter Reed General Hospital, Wash., D.C.

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Office of Biometry and Field Studies, NINCDS

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.1	.1	

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Photoelectric plethysmography was employed to record amplitude changes in pulsatile blood flow from each of the supraorbital fields during carotid compression in 75 patients scheduled for carotid angiograph. A testing method was developed on the basis of these data to detect carotid obstructive patients. The study result showed that with the developed method, 67 percent of the patients with radiologically significant carotid obstruction and 91 percent without it were correctly identified. It suggests that the developed method provides a rapid non-invasive test for unilateral carotid stenosis or occlusion. A report of this study was published in the March issue of the IEEE Transactions on Biomedical Engineering, 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02449-01 OBFS

PERIOD COVERED
October 1, 1979 through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Epidemiology of Disabling Headache

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Murray Goldstein, D.O., M.P.H., Deputy Director, NINCDS, NIH

P.I.: Ta-Chuan Chen, Ph.D., Mathematical Statistician, OBFS, NINCDS, NIH

COOPERATING UNITS (if any)

None

LAB/BRANCH
Office of the Director and Office of Biometry and Field Studies

SECTION
Office of the Deputy Director and Office of the Chief (OBFS)

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.30	PROFESSIONAL: 0.30	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An extensive collection and review of the published literature and reports on various aspects of epidemiology of Headache has been carried out in FY 1980. Strengths and inadequacies of the published information about prevalence, the characteristics of the afflicted population and the identification of risk factors that may be associated with both the occurrence of the headache syndrome or with its acute exacerbations were summarized and evaluated. Research approaches which can provide improved data for approaching the clinical issues of etiology, prevention and therapy were suggested. An invited paper of the review work was presented at the International Headache symposium 1980 in Florence, Italy, in March, 1980.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02238-04 OBFS

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Pilot Data Bank Project Network in Stroke (previously titled: Computerized Interactive Data Bank for Comprehensive Stroke Centers)

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Selma C. Kunitz, Head, Computer Applications Section, OBFS OD, NINCDS

Other: Cynthia Gross, Ph.D., Biostatistician, CAS, OBFS, OD, NINCDS
Barbara Nichols, Programmer, CAS, OBFS, OD, NINCDS
Sylvia Edelstein, CAS, OBFS, OD, NINCDS
Dr. Albert Heyman, Duke University Medical Center
Dr. Jay Mohr, University of South Alabama College of Medicine
Dr. Thomas Price, University of Maryland School of Medicine
Dr. Philip Wolf, Boston University Medical Center, School of Medicine

COOPERATING UNITS (if any)
Duke University Medical Center; Univ. of Maryland, School of Medicine; University of South Alabama, College of Medicine; Boston University Medical Center, School of Medicine

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Office of Biometry and Field Studies

SECTION
Computer Applications Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.2	.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A goal of developing a computerized interactive data bank for the Comprehensive Stroke Centers is to provide a development model for neurological diseases which will aid both the clinician and researcher in the treatment, prognosis, rehabilitation, and possible prevention of such diseases. The objectives of the project are: a. To develop a uniform method of data collection utilizing standard clinical nomenclature and vocabulary, patient histories, diagnosis, and treatment. b. To implement an interactive comprehensive data bank network enabling pooling of clinical data among institutions, collaborative inter-institutional studies, rapid access to large quantities of clinical data, and computer consultation. c. To demonstrate the feasibility of such a network, including the computer aspects, the collaboration among a number of institutions, to serve as a model for neurological diseases and disorders.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02443-01 OBFS

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Development of Offline Data Entry System for Stroke and Coma Projects

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Selma C. Kunitz, Head of Computer Applications Section,
OBFS, OD, NINCDS

P.I.: Barbara Nichols, Programmer, CAS, OBFS, OD, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Computer Applications Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	.8	.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A "front end" general purpose software package was developed for the Datapoint terminals for the Data Bank Centers, which allows data to be entered, edited, and stored locally by time and date. This software package also sorts the data and prepares it for subsequent transmission in a batch mode over a commercial line to the Stanford computer system which accomplishes more complex editing. The software operates with menu processing, in which a nonprogrammer can choose from the relevant form(s) for data entry from a list of options. It produces screen images which replicate the order of data on the data collection record. During data entry, data are edited for valid numeric ranges, alpha/numeric checks, code lists, and special formats such as dates.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02407-02 OBFS

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Assessment of Databank Methodology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Selma C. Kunitz, Head, Computer Applications Section
OBFS, OD, NINCDS

Other: Sylvia Edelstein, Chief Programmer, CAS, OBFS, OD, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Computer Applications Section, OBFS, OD, NINCDS

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.7	.5	.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A project to assess the computer methodology used in the Pilot Data Bank networks in Stroke and Traumatic Coma is proposed. Its purpose is to 1) compare the methodology (hardware and software) in these pilots to other available data base management systems, 2) develop specifications for modifying or replacing all or part of the current system, (TOD), in order to obtain a more optimal system, and 3) if appropriate, implementation of the specifications for an optimal data base management system for a National Databank for Neurologic Disorders.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02408-02 OBFS

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Clinical Databanks As a Resource for Epidemiologic Research

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Cynthia Gross, Ph.D., Biostatistician-Epidemiologist
Computer Applications Section, OBFS, OD, NINCDS

Other: Selma C. Kunitz, Head, Computer Applications Section,
OBFS, OD, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Computer Applications Section, OBFS, OD, NINCDS

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.3	.3	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Much has been written on the use of observational studies in epidemiological research. It will be necessary to apply many of the same epidemiologic techniques used in conventional observational studies to the clinical data bank. Work on determining which epidemiologic approaches are most appropriate for use with clinical data banks has begun in conjunction with the Stroke and Traumatic Coma Databank Networks (N01-NS-8-2396, 78, N01-NS-9-2302, 6, 7, 8, 9). A manuscript is being prepared for a computer applications in medical care publication.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02312-04 OBFS

PERIOD COVERED
October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)
Maternal Infection Study

FORMERLY: Methodology for Systematic Analysis of Multiple Antibody Readings on Matched Controlled Studies

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Jonas H. Ellenberg, Head, Section on Mathematical Statistics, OBFS, NINCDS
P.I. John L. Sever, Chief, Infectious Disease Branch, IRP, NINCDS

COOPERATING UNITS (if any)
Infectious Disease Branch, IRP, NINCDS

LAB/BRANCH
Biometry and Field Studies, Office of

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NIH, NINCDS, Bethesda, MD 20205

TOTAL MANYEARS: .2	PROFESSIONAL: .1	OTHER: .1

CHECK APPROPRIATE BOX(ES)
☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Analysis of the Collaborative Perinatal Project (CPP) Data continues in the area of maternal infection. [The CPP is a prospective study of approximately 60,000 gravidae and the follow-up of their children through the seventh year of life.] The relationship of maternal infection during pregnancy with the later status of the child is being examined using both serologically confirmed and clinically confirmed infections in the mother.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02347-03 OBFS

PERIOD COVERED
October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Observational Study of a Clinic Population of Cerebral Palsy Patients

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Leon Root, Director of CP Clinic, Hospital for Special Surgery, NYC, NY

PI: Robert Richter, Mathematician, Section on Mathematical Statistics,
OBFS, NINCDS

COOPERATING UNITS (if any)

Hospital for Special Surgery, NYC
Cerebral Palsy Clinic, Leon Root, Director

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NIH/NINCDS, Bethesda, MD 20205

TOTAL MANYEARS: 0	PROFESSIONAL: 0	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is an observational study of a large urban clinic population of cerebral palsy patients. The population to be examined consists of approximately 1,000 Cerebral Palsy patients of the Hospital for Special Surgery in New York City.

Staff of OBFS collaborated on the definition of the standardized vocabulary, designed the data collection protocols, and established a quality control mechanism for data collection. The Office of Biometry and Field Studies is no longer collaborating on this study.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02351-03 OBFS

PERIOD COVERED
October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Improving Current Methods of Analyzing Molecular Hybridization Experiments

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Rosalind B. Marimont, Research Mathematician, Section on Mathematical Statistics, OBFS, NINCDS

PI: Lawrence D. Grouse, Medical Officer, Laboratory of Developmental Neurobiology, NICHD

COOPERATING UNITS (if any)
Laboratory of Developmental Neurobiology, NICHD

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 0	PROFESSIONAL: 0	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Many hybridization experiments are analyzed by fitting the time curve of percent of DNA or RNA hybridized to various forms of the second order rate equation. Empirical correction factors must be applied for proper interpretation of results. Since the precise assumptions on which this method of analysis are based have not always been made clear, there is some uncertainty about applicability of particular equations. Also some laboratories lack sufficiently general curve fitting programs. The computer system MLAB, available at NIH and some other installations, has been recommended for its power and generally in curve fitting and model building. One simple but important question -- under what ranges of initial tracer to driver concentration are two of the commonly used approximations to the second order rate equation valid -- has been answered by computing and displaying the appropriate curves over a large range of initial concentrations. A paper has been submitted for publication. No further work is anticipated on this project.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02353-03 OBFS

PERIOD COVERED

October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Synthesis of Graph and Matrix Theory

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P. I.: Rosalind B. Marimont, Research Mathematician, Section on Mathematical Statistics, OBFS, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH

Biometry and Field Studies, Office of

SECTION

Mathematical Statistics

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 0	PROFESSIONAL: 0	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This was a long-term effort to combine the concepts and methodology of graph theory and matrix theory to facilitate understanding of and solution of a large class of problems for example, linear compartmental systems.

A previous matrix-graph theorem was extended. A series important in statistics was summed and its general behavior described by deriving its recursive form through graph-matrix methods.

Several other series were also shown to be expressible in recursive form, which greatly simplifies their computation. No further work is anticipated in this area.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02354-03 OBFS

PERIOD COVERED
October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Clinical Trial of Efficacy of Phenobarbital as Prophylaxis for Children with Febrile Seizures

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Roger J. Porter, Chief, Epilepsy Branch, NINCDS
P.I. Jonas H. Ellenberg, Head, Section on Mathematical Statistics, OBFS, NINCDS
P.I. Karin B. Nelson, Chief, Cerebral Palsy and Other Motor Disorders Section, DNB, NINCDS

COOPERATING UNITS (if any)
1. Cerebral Palsy and Other Motor Disorders Section, Developmental Neurology Branch, NINCDS
2. Epilepsy Branch, NINCDS

LAB/BRANCH
Biometry and Field Studies, Office of

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NIH, NINCDS, Bethesda, MD 20205

TOTAL MANYEARS: .1	PROFESSIONAL: .1	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Six percent of all children with febrile seizures are at relatively high risk for later afebrile activity. A proposal is being developed for a clinical trial which will examine the efficacy and toxicity of chronic and short-term prophylaxis for this group of children. At present chronic prophylactic medication is recommended by several authors without available information as to the potential success or side effects of such medication. The Developmental Neurology Branch, the Epilepy Branch, and the Office of Biometry and Field Studies have been working together on this ongoing project.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02409-02 OBFS

PERIOD COVERED

October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Image Reconstruction Theory

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Rodney A. Brooks, Physicist, Neuroradiology and Computed
Tomography Section, Surgical Neurology Branch, NINCDS
P.I. Alan J. Talbert, Statistician, OBFS, NINCDS

COOPERATING UNITS (if any)

Neuroradiology and Computed Tomography Section,
Surgical Neurology Branch, NINCDS

LAB/BRANCH
Biometry and Field Studies, Office of

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NIH, NINCDS, Bethesda, MD 20205

TOTAL MANYEAR: .1	PROFESSIONAL: .1	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Computer simulations of CT scans have been made in the development of an improved method of back projection in Computed Tomography. This method employs interpolation in both the ρ and ϕ polar coordinates. This project is a continuing collaboration.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02410-02 OBFS

PERIOD COVERED
October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Dual Energy Scanning

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Rodney A. Brooks, Physicist, Neuroradiology and Computed Tomography Section, Surgical Neurology Branch, NINCDS
P.I. Alan J. Talbert, Statistician, OBFS, NINCDS

COOPERATING UNITS (if any)

Neuroradiology and Computed Tomography Section,
Surgical Neurology Branch, NINCDS

LAB/BRANCH
Biometry and Field Studies, Office of

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NIH, NINCDS, Bethesda, MD 20205

TOTAL MANYEARS: .1	PROFESSIONAL: .1	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Methodology has been implemented for optimizing the use of dual energy x-ray scans to obtain information on chemical constituents of scan subjects. Two papers on this work have been published and a third paper has been submitted.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02411-02 OBFS

PERIOD COVERED

October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Survey of Management of Children with Febrile Seizures

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Jonas H. Ellenberg, Head, Section on Mathematical Statistics,
OBFS, NINCDS

P.I. Karin B. Nelson, Chief, Cerebral Palsy and Other Motor Disorders
Section, DNB, NINCDS

COOPERATING UNITS (if any)

Cerebral Palsy and Other Motor Disorders Section,
Developmental Neurology Branch, NINCDS

LAB/BRANCH

Biometry and Field Studies, Office of

SECTION

Mathematical Statistics

INSTITUTE AND LOCATION

NIH, NINCDS, Bethesda, MD 20205

TOTAL MANYEARS: .2	PROFESSIONAL: .1	OTHER: .1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

As a first step in considering an expensive and prolonged clinical trial of prophylactic treatment for febrile seizures, a survey of clinical practice is being implemented, to determine which medical discipline/s treat most children with febrile seizures, what criteria physicians employ to determine therapy, the regimens prescribed, and the specific goals of therapy. The resultant information will be used in determining the parameters of any future clinical trial. The survey instrument is in the clearance and testing phase.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02412-02 OBFS

PERIOD COVERED

October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Consensus Meeting on the Management of Children with Febrile Seizures

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Jonas H. Ellenberg, Head, Section on Mathematical Statistics, OBFS, NINCDS

P.I. Karin B. Nelson, Chief, Cerebral Palsy and Other Motor Disorders Section, DNB, NINCDS

COOPERATING UNITS (if any)

Cerebral Palsy and Other Motor Disorders Section,
Developmental Neurology Branch, NINCDS

LAB/BRANCH
Biometry and Field Studies, Office of

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NIH, NINCDS, Bethesda, MD 20205

TOTAL MANYEARS: .3	PROFESSIONAL: .2	OTHER: .1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Febrile seizures in young children are very common, affecting 3-4% of the pediatric population, yet up to now there was no consensus as to their optimal medical management. The possible consequences of febrile seizures, including their effect upon later physical and intellectual development and upon the likelihood of later chronic epilepsies, have been uncertain on the basis of available medical information. Since the use of chronic anticonvulsant medication may not be without risk in the very young child, it is necessary, in considering the need for treatment, to evaluate the risks in the natural history of the disorder. The next reasonable step is to consider the risks and benefits of chronic prophylaxis. The purpose of the consensus meeting was the reassessment of the available evidence in an effort to reach a rational policy of clinical management as guidance to the practicing community. The consensus statement concluded that the prognosis for children with febrile seizures was excellent and that there is no evidence that prophylaxis can prevent long-term sequelae. It excluded some 60% of all children with febrile seizures from any consideration of treatment.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02413-02 OBFS

PERIOD COVERED
October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Study of Lisuride for the Treatment of Parkinson Patients

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. D. Calne, Chief, Experimental Therapeutics Branch, IRP, NINCDS

Others: R. Giopinathan, Therapeutics Section, Experimental Therapeutics Branch, IRP, NINCDS
James Dambrosia, Mathematical Statistician, Section on Mathematical Statistics, OBFS, NINCDS

COOPERATING UNITS (if any)

Therapeutics Section, Experimental Therapeutics Branch, NINCDS

LAB/BRANCH
Biometry and Field Studies, Office of

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NIH, NINCDS, Bethesda, MD 20205

TOTAL MANYEARS: .1	PROFESSIONAL: .1	OTHER: 0

CHECK APPROPRIATE BOX(ES)

X (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The study was undertaken to determine the effectiveness of lisuride for the treatment of Parkinsonism. A reduction of rigidity, tremor, and akineasia was observed. Adverse reactions were also noted. The results of the study will appear in Neurology this year.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02414-02 OBFS

PERIOD COVERED

October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Simulation of Early Stopping Rules Used in Clinical Trials

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. James Dambrosia, Mathematical Statistician, Section on Mathematical Statistics, OBFS, NINCDS

P.I. Jonas H. Ellenberg, Head, Section on Mathematical Statistics, OBFS, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Biometry and Field Studies, Office of

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NIH, NINCDS, Bethesda, MD 20205

TOTAL MANYEARS: .1	PROFESSIONAL: .1	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In clinical trials with a specified survival time as the stated endpoint, a number of ad hoc statistical procedures have been proposed as guides to early trial termination. Distribution theory for these statistics is either mathematically intractable or only known asymptotically. A computer simulation study for comparison of the various procedures is being conducted. OBFS is organizing two sessions at the Spring 1981 Biometrics meetings concerning this topic.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02415-02 OBFS

PERIOD COVERED

October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Cage Standards for Primates

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Amos Palmer, Research Veterinarian, Infectious Diseases Branch, IRP, NINCDS

Other: James Dambrosia, Mathematical Statistician, Section on Mathematical Statistics, OBFS, NINCDS

COOPERATING UNITS (if any)

Infectious Diseases Branch, NINCDS

LAB/BRANCH

Biometry and Field Studies, Office of

SECTION

Mathematical Statistics

INSTITUTE AND LOCATION

NIH, NINCDS, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.1	.05	.05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Present cage assignments for primates are based solely on the animals' weight. Variation in shape between species of primates of the same weight indicate that the current weight-based standard may be inappropriate. A large number (410) of primates of four different species have been measured (arms, legs, chest, tail, crown to rump, crown to heel) in order to determine association of and variations in weight as functions of shape measurements. A paper on this topic has been submitted for publication.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02417-02 OBFS

PERIOD COVERED

October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Doubly Linked List Processing Algorithm

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Alan J. Talbert, Statistician, Section on Mathematical Statistics,
OBFS, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH

Biometry and Field Studies, Office of

SECTION

Mathematical Statistics

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 0	PROFESSIONAL: 0	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An algorithm was devised to process a doubly linked list by computer. Such lists are useful in applications requiring insertion and deletion of list items at arbitrary positions in a list sorted by ascending keys. Processing is simpler than for trees and is preferable for small lists. This capability facilitated computations of overlapping session times in a survey of computer terminal usage. This project has been completed.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02418-02 OBFS

PERIOD COVERED

October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Elective Hysterectomy and Antibiotics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.: Robert Richter, Mathematician, Section on Mathematical Statistics, OBFS, NINCDS

P.I.: Jonas H. Ellenberg, Head, Section on Mathematical Statistics, OBFS, NINCDS

P.I.: John H. Grossman III, Assistant Professor, OBS-GYN, Guest Worker Infectious Diseases Branch, NINCDS

COOPERATING UNITS (if any)

George Washington Medical Center, OBS-GYN
Infectious Diseases Branch, IRP

LAB/BRANCH

Biometry and Field Studies, Office of

SECTION

Mathematical Statistics

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 0	PROFESSIONAL: 0	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project involves the study of the effects of antibiotics on bacterial infections in 100 women undergoing elective hysterectomy in the Yale-New Haven Hospital from 1973 to 1977. Antibiotics used were Penicillin and Cefazolin.

Staff members of OBFS collaborated on the extensive data analysis, including multivariate analysis of variance for categorical data. The project has been completed.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02420-02 OBFS

PERIOD COVERED

October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Minicomputer Acquisition

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Robert Richter, Mathematician, Section on Mathematical Statistics, OBFS, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Biometry and Field Studies, Office of

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NIH, NINCDS, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.20	.20	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project involved the procurement of an HP-1000 minicomputer. An OBFS staff member collected and analyzed statistical and graphics requirements from each OBFS section and translated these needs into hardware and software requirements. An intensive search of commercial and governmental resources (including NIH's) yielded three sources -- IBM, Digital Equipment Company, and Hewlett Packard (HP) -- that met most requirements. The HP-1000 minicomputer was selected and an initial configuration was designed, purchased, and delivered.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02421-02 OBFS

PERIOD COVERED
October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Assessment of Robustness of Missing Data Techniques

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Jonas H. Ellenberg, Head, Section on Mathematical Statistics,
OBFS, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Biometry and Field Studies, Office of

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NIH, NINCDS, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.20	.10	.10

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Several techniques for handling missing observations in the statistical analysis of large data sets have been proposed. All of the existing techniques require certain assumptions about the underlying model; generally this includes the assumption that the missing data are randomly generated and randomly dispersed within the data set. This project is assessing the robustness of the standard techniques to variations in the underlying assumptions, such as nonrandomness and high intercorrelations within the data set. The project will be accomplished using computer simulation on our HP-1000 minicomputer.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02340-03 OBFS

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Pilot Data Bank Network Project in Coma

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Selma C. Kunitz, Chief, Computer Applications Section, OBFS, OD, NINCDS

Other: James M. Dambrosia, Ph.D., Mathematical Statistician,
Section on Mathematical Statistics, OBFS, OD, NINCDS
Cynthia Gross, Ph.D., Biostatistician, CAS, OD, NINCDS
Sylvia Edelstein, Systems Analyst, CAS, OD, NINCDS
Barbara Nichols, Programmer, CAS, OD, NINCDS
Dr. Lawrence Marshall, University Hospital at San Diego, CA
Dr. Howard Eisenberg, University of Texas Medical Branch at Galveston, Texas
Dr. John Jane, University of Virginia Medical Center, Charlottesville, VA
Dr. Douglas Miller, Medical College of Virginia, Richmond, VA

COOPERATING UNITS (if any)
University Hospital at San Diego, CA; University of Texas Medical Branch at Galveston, Texas; University of Virginia Medical Center, Charlottesville, VA; Medical College of Virginia, Richmond, VA

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Computer Applications Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .8	PROFESSIONAL: .6	OTHER: .2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A pilot multicentered interactive data bank project restricted to traumatic coma has been implemented. The objectives of the study are:

1. To utilize a uniform clinical vocabulary and method of data input
2. To evaluate the feasibility of a multicentered traumatic coma data bank system to examine:
   a. The ability of diverse institutions to participate and collaborate effectively
   b. The ability to collect data of high quality
   c. The ability to insure the quality and quantity of data from diverse institutions
   d. The preliminary utility of the data for patient management and in indicating research leads
   e. The ability to provide guidelines and protocols for expansion to additional centers and other neurologic disorders.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02444-01 OBFS

PERIOD COVERED
October 1, 1979, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Cognitive and Behavioral Effects of Phenobarbital in Young Children

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Karin Nelson, Chief, Cerebral Palsy and Other Motor Disorders Section, DNB, NINCDS

P.I. Deborah Hirtz, Neurologist, Cerebral Palsy and Other Motor Disorders Section, DNB, NINCDS

P.I. Jonas H. Ellenberg, Head, Section on Mathematical Statistics, OBFS, NINCDS

COOPERATING UNITS (if any)
Cerebral Palsy and Other Motor Disorders Section, DNB, NINCDS

LAB/BRANCH
Biometry and Field Studies, Office of

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NIH, NINCDS, Bethesda, MD 20205

TOTAL MANYEARS: .1	PROFESSIONAL: .1	OTHER: .0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project evaluates the short-term cognitive and behavioral effects of continuous phenobarbital therapy in children with febrile seizures. The study is designed to detect differences, if they exist, in measures taken before and after initiation of therapy.

HEW-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02445-01 OBFS

PERIOD COVERED
March 1, 1980, through September 30, 1980

TITLE OF PROJECT (80 characters or less)

A Clinical Trial of Bromocriptine and Lisuride for the Treatment of Parkinson Disease

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. J.M. Dambrosia, Mathematical Statistician, OBFS, NINCDS
P.I. Donald Calne, Head, Experimental Therapeutics Branch, IR, NINCDS

COOPERATING UNITS (if any)

Experimental Therapeutics Branch, IRP, NINCDS

LAB/BRANCH
Biometry and Field Studies, Office of

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NIH, NINCDS, Bethesda, MD 20205

TOTAL MANYEARS: .5	PROFESSIONAL: .4	OTHER: .1

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project accesses the efficacy of Lisuride versus Bromocriptine for the treatment of Parkinson's disease. A randomized, double blind, two-period crossover clinical trial is employed to evaluate the effectiveness of treatment of thirty outpatients. Patient responses (tremor, rigidity, and akinease) are measured using the Columbia rating scale. Adverse reactions are also monitored.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02446-01 OBFS

PERIOD COVERED

July 1, 1980 through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Parkinson Twin Studies

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Christoper Ward, Neurologist, Experimental Therapeutic Branch, IRP, NINCDS
P.I. J.M. Dambrosia, Mathematical Statistician, OBFS, NINCDS
P.I. Rosewell Eldridge, IRP, NINCDS

COOPERATING UNITS (if any)

Experimental Therapeutics Branch, IRP, NINCDS
Section on Epidemiology, IRP, NINCDS

LAB/BRANCH
Biometry and Field Studies, Office of

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NIH, NINCDS, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.25	.10	.15

CHECK APPROPRIATE BOX(ES)

X (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The project studies twin pairs, discordant with respect to Parkinsonism, to determine clinical differences, environmental differences, and other factors that may be associated with Parkinson's disease. The clinical and zygoticity evaluations are current, but much of the data is obtained retrospectively. OBFS will maintain the data set and is responsible for all analysis.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02447-01 OBFS

PERIOD COVERED

July 1, 1980 through September 30, 1980

TITLE OF PROJECT (80 characters or less)

A Prospective Study of Low Birthweight Infants

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. J.M. Dambrosia, Mathematical Statistician, OBFS, NINCDS
P.I. Karin Nelson, Chief, Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS

COOPERATING UNITS (if any)

Children's Hospital of Washington, DC
Section on Cerebral Palsy and Other Motor Disorders, DNB, NDP, NINCDS

LAB/BRANCH
Biometry and Field Studies, Office of

SECTION
Mathematical Statistics

INSTITUTE AND LOCATION
NIH, NINCDS, Bethesda, MD 20205

TOTAL MANYEARS: .25	PROFESSIONAL: .15	OTHER: .10

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

All low birthweight (1750gm or less) infants referred to Children's Hospital are examined, CAT scanned for hemorrhage, and evaluated by the Hospital staff. Specified information is collected prospectively on each child until the age of three years. The objective of the study is to identify risk factors associated with neurological deficits, in particular CP.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02237-04 OBFS

PERIOD COVERED

October 1, 1979 through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Development and Design of a Pilot Study for a National Survey of Epilepsy

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Dallas Anderson, Survey Statistician, Section on Disease Statistics Surveys, OBFS, NINCDS

Other: Frederic Weinfeld, Head, Section on Disease Statistics Surveys, OBFS, NINCDS

COOPERATING UNITS (if any)

W. Allen Hauser, Dept. of Neurology, St. Paul-Ramsey Hospital,
St. Paul, Minn. 55101
Joseph Steinberg, Survey Design, Inc.

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS: .70	PROFESSIONAL: .50	OTHER: .20

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This pilot was initiated to develop a new and untried method of ascertaining the incidence and prevalence of epilepsy. The previously used methods have serious deficiencies and this proposal seeks to remedy them. The goal is to use pharmacies filling anticonvulsive prescriptions to lead to the physicians providing care and thus to the epileptics. By using nationwide probability sampling techniques, valid estimates of the U.S. epileptic population should be made. The contract was let and the pilot study is about to get underway.

NIH-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02239-04 OBFS

PERIOD COVERED

October 1, 1979 through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Design of Convulsive Disorder Questionnaires

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Frederic Weinfeld, Chief, Surveys and Demographic Studies Section, OBFS, NINCDS

COOPERATING UNITS (if any)

Clint Burnham, Health Interview Survey, NCHS
W. Allen Hauser, Dept. of Neurology, St. Paul-Ramsey Hospital
St. Paul, Minn. 55101

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.5	.5	

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☒ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The design and field testing of questionnaires to be used as a supplement to the NCHS Health Interview Survey (HIS). The first was designed to determine the persons with some degree of stroke, diagnosed or undiagnosed; and hospitalization. This questionnaire was included in the 1977 HIS. A second has been designed to measure those persons with convulsive disorder and is being proposed for a future HIS. The stroke questionnaire has been submitted to NCHS and is included in their current household interview survey.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02341-03 OBFS

PERIOD COVERED

October 1, 1979 through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Type-Specific Stroke Mortality Trends
(Previously titled: "Stroke Mortality Study")

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Herbert M. Baum, Ph.D., Survey Statistician, OBFS, NINCDS

PI: Murray Goldstein, D.O., Associate Director, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.30	.20	.10

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

There is a need to examine stroke mortality trends by specific types of strokes. OBFS has obtained the mortality data tapes for 1968-1976, and used these tapes to examine age-type-specific stroke trends by race, sex, and hypertension status. There are many problems inherent in such a study, but the results would be useful to health planners and administrators. Additionally, this study will be useful in generating hypotheses OBFS may be interested in examining at a later date.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02442-01 OBFS

PERIOD COVERED
October 1, 1979 - September 30, 1980

TITLE OF PROJECT (80 characters or less)

Feasibility of A National Survey of Speech Defects

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Herbert M. Baum, Ph.D., Survey Statistician, OBFS, NINCDS

PI: Christy Ludlow, Ph.D.,Research Speech Pathologist, CDP, NINCDS

COOPERATING UNITS (if any)

Communicative Disorders Program, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies, OD, NINCDS

SECTION
Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland, 20205

TOTAL MANYEARS: .12	PROFESSIONAL: .10	OTHER: .02

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

National data on communicative disorders is quite scarce. With instruments recently developed by the Institute, a valid test is now available. What needs further clarification is how these instruments could be used for a national study of communicative disorders.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02401-02 OBFS

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

The Relationship Between Stroke and Speech and Hearing Defects

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Herbert M. Baum, Ph.D., Survey Statistician, OBFS NINCDS

PI: Christy L. Ludlow, Ph.D., Research Speech Pathologist,
Communicative Disorders Program, NINCDS

COOPERATING UNITS (if any)

Communicative Disorders Program, NINCDS

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.0		

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The 1977 Health Interview Survey had supplements on hearing and stroke. The data on these disorders are to be analyzed in conjunction with what is regularly collected about speech defects. The analysis will yield estimates on the complications resulting from stroke and we will examine whether these complications can be used as an indicator for stroke in interview surveys.

An examination of the data revealed that for the type of analysis needed, the number of cases was too small for meaningful conclusions to be drawn. The project is therefore concluded.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02402-02 OBFS

PERIOD COVERED
October 1, 1979 through September 30, 1980

TITLE OF PROJECT (80 characters or less)

An Examination of Speech and Hearing Problems andDetected in Hanes II

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Christy L. Ludlow, Ph.D., Research Speech Pathologist, Communicative Disorders Program, NINCDS

PI: Herbert M. Baum, Ph.D., Survey Statistician, Section on Surveys and Demographic Studies, OBFS NINCDS

COOPERATING UNITS (if any)

Communicative Disorders Program, NINCDS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.0		

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The Communicative Disorders Program anticipates conducting a survey of speech disorders among 2-6 year olds. Current work is focusing on constructing a valid test instrument. Concurrently, our Office is assisting in examining similar work done by the HANES II. We intend to use the experience and results from the HANES to determine the feasibility of the survey and what problems should be avoided. We are so exploring the possibility of conducting the survey as part of a future phase of the HANES.

A review of the Hanes Project was undertaken. The investigators have determined that the NCHS methodology is not applicable to our work and that we will have to develop an independent approach. This project is therefore concluded.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 NS 02403-02 OBFS

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

The Incidence and Prevalence of Stroke

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Frederic D. Weinfeld, Ed.D., Head, Section on Surveys and Demographic Studies, OBFS, NINCDS

PI: Herbert M. Baum, Ph.D., Survey Statistician, OBFS, NINCDS

COOPERATING UNITS (if any)

Morton Robins, Project Director, Nationwide Study of Stroke, Westat Inc., Rockville, MD

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.25	.15	.10

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Estimates of the incidence and prevalence of stroke were generated from the findings of the National Study of Stroke. Thses are being prepared for publication as a journal article, and for the comparison with other commonly accepted estimates of incidence and prevalence.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02405-02 OBFS

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Assessment of Strategies for Analyzing Data from Small Area Mortality Surveys

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Dallas W. Anderson, Ph.D., Section on Surveys and Demographic Studies, OBFS, NINCDS

COOPERATING UNITS (if any)

W. Edwards Deming, Ph.D., Consultant in Statistical Studies, Washington, D.C.

LAB/BRANCH
Office of Biometry and Field Studies,

SECTION
Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.09	.01

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Studies of small areas, such as communities or counties, are an important tool of epidemiologists, who are interested in studying the distribution of particular diseases in populations. Many studies of this type have been reported in the scientific literature. An assessment of techniques of analysis frequently used in these studies was initiated to determine their adequacy for use in the NINCDS survey of major neurological disorders in Copiah County, Mississippi (Y01-NS-70031, N01-NS-7-2357).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02006-02 OBFS

PERIOD COVERED
October 1, 1979 through September 30, 1980

TITLE OF PROJECT (80 characters or less)

The Frequency of Neurological Disorders Among Hospital Discharges

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Herbert M. Baum, Ph.D., Survey Statistician, OBFS, NINCDS

COOPERATING UNITS (if any)

Dr. Donald Smith, Hospital Care Statistics Branch, NCHS

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Section on Surveys and Demographic Studies

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.15	.10	.05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The Hospital Care Statistics Branch has agreed to provide us with data on hospital discharges where a neurological disorder is indicated. A list of ICDA codes has been prepared of conditions of primary interest to the Institute. By examining the data on the first discharge diagnosis and on all listed discharge diagnoses we intend to examine the time trends. In addition, by constantly updating the data, we intend to be able to handle requests for data on the hospitalization of neurological conditions. This has now become an annual reporting effort.

ANNUAL REPORT

October 1, 1979 through September 30, 1980

Extramural Activities Program

National Institute of Neurological and Communicative Disorders and Stroke

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Director's Report
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Extramural Activities Program (EAP), NINCDS, was organized in July, 1975, to serve as the Institute center for science administration and fiscal management of the grant, fellowship, and research contract programs. The structure of EAP includes components responsible for manpower, scientific merit review, contract management, grants management, committee management, data reporting and analysis, and program support services including processing.

The senior staff of EAP consists of:

Director
Deputy Director
Chief, Scientific Evaluation Branch
Chief, Contracts Management Branch
Chief, Grants Management Branch
Chief, Office of Data Analysis and Reports

Staff carries out an overall coordinating and supervisory function in regard to the implementation of recommendations of the NANCDS Council and Contract Advisory Committees, and the processing and issuance of proposals and awards in the respective program areas. The Director, EAP, in consultatation with the Director of NINCDS, works closely with the other Program Directors on questions of policy relating to the NINCDS extramural programs.

More specifically, the Extramural Activities Program coordinates grant and contract programs for the NANCDS Council, the Program Directors, the Contract Review Board, the Training Board, the Program Staff, and the Extramural Staff. The EAP studies and supervises certain program processes, e.g., distribution of awards during the four quarters of the fiscal year; prepares summary data, e.g., the Research Grant and Fellowship Data Books; and provides fiscal information, e.g., Fiscal Status Reports, Percentage Funding Rates, and develops alternate strategies for various budget levels.

The major personnel changes are as follows: Dr. John W. Diggs, formerly Chief, Scientific Evaluation Branch, was named Deputy Director of the EAP. Dr. Diggs replaces Dr. O. Malcolm Ray, who now serves as Chief, Office of Program Planning and Evaluation. Dr. Raymond Summers, formerly Assistant Director for Manpower Programs, was appointed Chief, Scientific Evaluation Branch.

In summary, the Extramural Activities Program provides for the Director of the Institute and the Directors of the Program Areas scientific, fiscal, and administrative management support services.

ANNUAL REPORT
October 1, 1979, through September 30, 1980
Research Grants Program
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Research Grants portion of the NINCDS Annual Report provides an overall summary of administrative developments as they pertain to research grants. Other activities such as training awards, contracts, etc., are mentioned here merely to provide an overview, and are discussed in more detail elsewhere.

The research grant, contract, and training programs of the NINCDS are focused on the identification, stimulation, and support of essential research problems aimed at the improved diagnosis, treatment, and prevention of disorders of the nervous system, the neuromuscular apparatus, the ear, and human communication. They include disorders affecting the development and maturation of the nervous system (developmental disorders, motor and convulsive disorders, and demyelinating and degenerative disorders); disorders caused by extrinsic insults (central nervous system infections, stroke, trauma, neoplasms); and disorders in human communication (hearing, speech, language, the vestibular system, other senses, and behavior). Research support is also provided in the area of fundamental neuroscience which is appropriate to the Institute's mission, but not related to any specific disorder. Included are nerve structure and function studies and investigations of the development of various types of prostheses. The administrative instruments used to accomplish these purposes include research projects, research program projects, clinical research centers, research career awards, research career development awards, teacher-investigator awards, institutional research fellowship awards, individual research fellowship awards, and contracts.

The following Table shows the number of research grant applications considered by the Council at its spring meetings over the past five years.

JUNE '75	SEPT. '76*	MAY ' 77	MAY '78	MAY '79	MAY '80
481	493	574	600	645	618

*Comparable to a spring meeting on the basis of the new fiscal year.

Compared to the same time period in 1975, there has been a significant increase in the number of applications reviewed. This may be attributed partially to the effectiveness of the research training programs of the Institute from which the output of fully trained investigators has reached its full potential only in recent years. The large increase that occurred in May, 1977, is probably due largely to the fact that for the previous year or two it was possible to fund only 25-30 percent of the approved applications. A large proportion of the unfunded applicants reapply, thus increasing the number of applications to be reviewed.

The following Table shows the number of research grants awarded and the total amounts of funds expended (in millions) each year for the past five years.

	FY '76**	FY '77	FY '78	FY '79	FY '80
NUMBER*	1,244	1,154	1,284	1,554	1,697
DOLLARS*	$89.1	$99.0	$110.9	$138.4	$160.5

*Includes RCDAs and TIAs
**Exclusive of Transition Quarter

From FY '76 to FY'78 there was a gradual increase in the funds available. However, the number of grants awarded did not increase, presumably because of inflation, increases in indirect costs, and other increases in the cost of doing research. For the current year (FY '80) there was an increase of 16 percent in the amount of funds available and an increase of 9 percent in the number of grants awarded.

Table I (on the following page) shows the number of awards and the amounts of funds expended for each type of award within each Program Area.

TABLE 1

Number of Awards and Dollars* Expended by Program Area and Type of Award

TYPE OF AWARD	PROGRAM AREAS								TOTAL	
	CD		FN		ND		ST			
	No.	Dollars	No.	Dollars	No.	Dollars	No.	Dollars	No.	Dollars
Research Grants (R01)	273	$20.414	371	$24.700	629	$44.552	158	$12.705	1,431	$102.371
Program Projects (P01) and Clinical Centers (P50)	14	8.774	10	3.364	29	16.688	42	22.692	95	51.518
Contracts (N01)	15	1.410	22	1.941	20	5.215	8	2.853	65	11.419
Training Grants (T32)	15	1.036	23	2.001	22	1.739	5	.431	65	5.207
Fellowships (F32)	40	.781	77	1.424	58	1.093	13	.248	188	3.546
Teacher Investigator Awards (K07)	17	.699	--	--	41	1.727	15	.618	73	3.044
Research Career Development Awards	19	.714	23	.840	45	1.642	11	.399	98	3.595
Research Career Awards (K06)	1	.034	--	--	3	.099	1	.032	5	.165
GRAND TOTAL	394	$33.862	526	$34.270	847	$72.755	253	$39.978	2,020	$180.865

*Dollars in millions

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Manpower Programs' Report
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Institute has four training programs. Two programs, the Individual National Research Service Award Program and the Institutional National Research Service Award Program, are funded from the $8.912 million available in the FY '80 budget for training. The other two programs, the Research Career Development Award Program and the Teacher Investigator Development Award Program, are funded from FY '80 funds available for research grants in the "other" category.

In accordance with the Biomedical Research and Research Training Amendments of 1978, several changes were announced in the National Research Service Awards (NRSA) programs. The most important of these changes, an increase in trainee stipends, became effective on July 1, 1980. In addition to increases in stipends, environmental support as of July 1, is awarded on the basis of $3,000/predoctoral trainee plus $5,000/postdoctoral trainee. The FY '80 budget for training included additional dollars in an approximate amount necessary to continue the NRSA programs at the current level, taking these increases into consideration.

The Biomedical Research and Research Training Amendment of 1978 also eliminated the requirement that NRSA trainees who receive support for training programs of three months or less sign a payback agreement. This new policy enabled the Institute to support short-term training programs. During the summer of 1980, two such programs became operational; one at the Marine Biological Laboratory, Woods Hole, Massachusetts, and another at the Cold Spring Harbor Laboratory, Cold Spring Harbor, New York.

In August, 1979, the National Institutes of Health announced a program for awarding National Research Service Awards to Senior Fellows. This program is somewhat similar to the Institute's old Special Traineeship Program. The program is especially appropriate for individuals who wish to obtain specialized training during a sabbatical period. During FY '80, the Institute made its first award under this new program.

The remainder of this report concerns the specifics of the four program areas:

National Research Service Awards for Institutional Grants (Training Grants)

From FY '80 funds, the Institute provided continuation support for 40 NRSA programs and made 25 new and renewal awards to support the following number of programs, according to NINCDS Program Area:

Program Area	New, Renewal & Supplemental Awards		Continuation Awards		Total	
	Number	Amount*	Number	Amount*	Number	Amount*
Communicative Disorders	4	$ 293	11	$ 743	15	$1,036
Fundamental Neurosciences	9	599	14	1,402	23	2,001
Neurological Disorders	11	881	11	858	22	1,739
Stroke and Trauma	1	89	4	342	5	431
Total	25	$1,862	40	$3,345	65	$5,207

*Amounts in thousands

In the training grant program, funds are being provided for 73 predoctoral trainees and 231 postdoctoral trainees. In addition, about 92 short-term trainees were supported in summer programs.

National Research Service Awards for Individual Postdoctoral Fellows (Fellowships)

From FY '80 funds, the Institute provided continuation support for 147 fellows and made 41 new and renewal awards. A number of supplemental awards were also made but this did not increase the number of individuals being trained. NINCDS made awards to support the following number of fellows, according to NINCDS Program Area:

Program Area	New, Renewal & Supplemental Awards		Continuation Awards		Total	
	Number	Amount*	Number	Amount*	Number	Amount*
Communicative Disorders	7	$ 184	33	$ 597	40	$ 781
Fundamental Neurosciences	26	534	51	890	77	1,424
Neurological Disorders	6	178	52	915	58	1,093
Stroke and Trauma	2	60	11	188	13	248
Total	41	$ 956	147	$2,590	188	$3,546

*Amounts in thousands

Research Career Development Award Progam

During the period covered by this report, NINCDS made the following number of new and continuation RCDAs, according to the NINCDS Program area:

Program Area	New Awards		Continuation Awards		Total	
	Number	Amount*	Number	Amount*	Number	Amount
Communicative Disorders	3	$ 113	16	$ 601	19	$ 714
Fundamental Neurosciences	4	143	19	697	23	840
Neurological Disorders	6	219	39	1,423	45	1,642
Stroke and Trauma	0	0	11	399	11	399
Total	13	$ 475	85	$3,120	98	$3,595

*Amounts in thousands

Teacher Investigator Development Award Program

During the period covered by this report, NINCDS made the following number of new and continuation TIDAs, according to NINCDS Program Area:

Program Area	New Awards		Continuation Awards		Total	
	Number	Amount*	Number	Amount*	Number	Amount*
Communicative Disorders	4	$ 63	13	$ 536	17	$ 699
Fundamental Neurosciences	0	0	0	0	0	0
Neurological Disorders	12	506	29	1,221	41	1,727
Stroke and Trauma	3	130	12	488	15	618
Total	19	$ 799	54	$2,245	73	$3,044

*Amounts in thousands

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October 1, 1979 through September 30, 1980
Grants Management Branch
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Grants Management Branch (GMB) consists of two sections, the Grants Administration Section and the Grants Processing Section. The Grants Administration Section consists of ten people and the Grants Processing Section consists of twelve people.

During fiscal year 1980, the GMB was responsible for a grant budget in excess of $176 million, of which approximately $167 million was for research and $9 million was for training. Compared to fiscal year 1979, this represented a 22% increase in the total grant budget with a 24% increase in the research budget and a 3% increase in the training budget. From the fiscal year 1980 grant budget, it is anticipated that approximately 2,200 awards will be made which would represent an increase of 10% in the total number of awards issued in fiscal year 1979. Since FY'77 the grant budget the GMB is responsible for has increased by 66% (from $106 million to the present $176 million); during the same period the number of awards issued has increased by 46% (from 1,490 to the present 2,200).

During fiscal year 1980, the GMB instituted a review of the Report of Research Grant Expenditures for the Research Career Development Awards, the Research Career Awards, and the Teacher-Investigator Development Awards. As a result, the GMB has been able to apply savings of approximately $55,000 to the awards for the above referenced programs.

During fiscal year 1980, the GMB continued to increase its interaction with the Scientific Evaluation Branch (SEB). This interaction has become more necessary and frequent with the introduction of more administratively complex programs by the Institute such as Positron Emission Transverse Tomography, the Huntington's Disease Centers Without Walls, and the X-ray Microbeam Tracking System. The introduction of the large and complex programs has also increased the Branch's interaction with the programs from the preparation of the program announcement through the award and administration of these grants.

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Contracts Management Branch
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Contracts Management Branch (CMB) consists of the Chief of the Branch, four contract specialists, and three supporting staff.

During the fiscal year 1980, the CMB was responsible for some 85 contracts and Interagency Agreements, totaling $15 million in awards. The total value of these contracts, including amounts obligated to-date, is nearly $60 million. In addition, there are some 85 research contracts that have expired and are in the process of being administratively closed out.

The CMB expects to award approximately 23 new contracts during FY 1980. Added to this workload are 60 renewals of existing contracts and over 100 actions not involving funds by modifying contracts in some other manner.

During FY 1980, the Secretary's Procurement Plan was put into effect. Part of this plan restricted the contracting offices to spend no more than 30 percent of their total contract appropriation in the fourth quarter and no more than 12 percent in each of the three months of the fourth quarter. The Branch was able to meet these goals, spending approximately 82 percent of its funds before July 1, 1980.

The CMB coordinates with the Division of Contracts and Grants (DCG) the training of NINCDS project officers in accordance with the Department-wide requirement for training of Program personnel serving in this capacity. Nearly all of the Institute's current project officers have now received this training. This training includes the HHS project officer training course, as well as that for Civil Rights Contract Compliance.

FY 1980 ANNUAL REPORT
October 1. 1979. through September 30. 1980
Office of Data Analysis and Reports
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Office of Data Analysis and Reports (ODAR) continues to perform the same functions as in the past and has added a major new activity this year--responsibility for maintaining and analyzing budget information for the Extramural Activities Program (EAP). The position of Budget Officer (EAP) was not filled when the incumbent left the Institute. Her duties were assigned to ODAR. In conjunction with this change the position of budget assistant was reassigned to this office.

The computerized information system for contracts is being used to issue recurring reports on both active contracts and Requests for Proposals (RFP's). Some additional report formats have been developed. A new computerized interactive travel system was also developed during the year. This will enable the Administrative Office to track extramural travel activities.

The office continues to publish on an annual basis the Training Data Book, the Fiscal Year Summary Book Series and the NINCDS Index to Research Grants and Contracts and on a semi-annual basis the Research Grants Data Book.

In addition to the budget assistant referred to above, a program analyst has also joined the staff which now consists of 4 program analysts, a budget assistant, 2 computer programmers, 2 grants clerks, and a clerk-typist.

ANNUAL REPORT
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Scientific Evaluation Branch
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Scientific Evaluation Branch (SEB) is responsible for the technical merit review of applications which are received primarily for the support of Program Projects, Specialized Centers, Conferences, Teacher-Investigator Development Awards, and Institutional National Research Service Awards. The Branch has three standing Committees -- Communicative Disorders Review Committee (CDRC), Neurological Disorders Program Project Review A Committee (NSPA), and Neurological Disorders Program Project Review B Committee (NSPB). Although these three committees are responsible for the technical merit review of the majority of grant applications, it is necessary to convene a number of other committees to evaluate applications not assigned to a standing committee. The Branch is also responsible for the technical merit review of all proposals submitted in response to a "Request for Proposal" (RFP) which requires assembling a number of other technical merit review panels.

On September 30, 1980 the staff of the Scientific Evaluation Branch included the following individuals:

Ellen Archer, Executive Secretary
Alfred Bruner, Executive Secretary
Diane Casillas, Grants Assistant
Margaret Caudle, Grants Technical Assistant
Leon J. Greenbaum, Jr., Executive Secretary
Frances Hisaoka, Grants Assistant
Joyce Lamb, Grants Technical Assistant
Ernest J. Moore, Executive Secretary
Meigs Phelan, Lead Contracts/Grants Technical Assistant
Raymond Summers, Chief
Howard Weinstein, Executive Secretary
Arthur B. White, Executive Secretary
Olga Williams, Grants Clerk

At the time this report is being prepared, individuals have not been selected to fill two additional positions, a grants technical assistant for the NSPA Committee and a part time clerical position.

The following table summarizes the number and type of grant applications that were reviewed, according to the type of review committee, and it indicates the number of site visits that were made.

NUMBER OF APPLICATIONS REVIEWED AND SITE VISITS MADE BY SCIENTIFIC EVALUATION BRANCH ACCORDING TO TYPE OF APPLICATION AND TYPE OF REVIEW GROUP

Type of Grant Application	Reviews by Standing NINCDS Committees (CDRC, NSPA and NSPB)		Reviews by Other Groups (NSS, SRC, and SSS)	
	Number of Applications	Number of Site Visits	Number of Applications	Number of Site Visits
Program Project (P01)	38	36	13	13
Exploratory Grant (P20)	1	0	0	0
Specialized Center (P50)	7	2	7	3
Research Grant (R01)	1	0	0	0
Cooperative Clinical Research Grant (R10)	0	0	6	5
Conference Grant (R13)	0	0	10	0
Teacher-Investigator Development Award (K07)	59	0	4	0
Institutional National Research Service Award (T32)	36	7	1	0
TOTAL	142	45	41	21

The table shows that 183 grant applications were reviewed and that 66 site visits were made. This is an increase of two applications over FY '79 and the number of site visits that were made is the same as the number made in FY '79.

Concerning the technical merit review of contract proposals, that were submitted in response to RFP's, 49 were received in response to 14 RFP's and the evaluation of these proposals involved three site visits. We anticipate receiving responses to one additional RFP (80-12) and we intend to evaluate these prior to the end of the fiscal year.

Personnel in the Scientific Evaluation Branch work closely with all components of the Extramural Activities Program and with personnel in the four NINCDS programs. It is imperative that we maintain liaison with leaders of the scientific community for the purpose of identifying the most qualified individuals to serve on our technical merit review committees and panels.

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Communicative Disorders Program
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Communicative Disorders Program
National Institute of Neurological and
Communicative Disorders and Stroke

Introduction

The Communicative Disorders Program of the National Institute of Neurological and Communicative Disorders and Stroke is responsible for the encouragement and support of research and training in the areas of balance, hearing, language, speech and the special senses (taste, smell, touch and pain). These areas are subdivisions of the general area of human communication.

Disorders of communication are very commonly encountered, constituting a major cause of impairment and handicap in our society. The economic impact of communication disorders upon the individual, in terms of employment disadvantage and quality of life, are considerable; the impact upon the nation as a whole, in terms of the costs of treatment rehabilitation and special education, are enormous.

Communicative Disorders Program Staff

Ralph F. Naunton, M.D., (formerly Professor of Surgery (Otolaryngology) and Chairman of Otolaryngology at the University of Chicago), while appointed in late 1979, was unable to assume his position as Program Director until June 1980.

As a result of an Intergovernmental Personnel Act Agreement (IPA) Molly Jones, Ph.D., worked with the Program between March and May of 1980, serving as a Health Scientist Administrator with particular responsibilities in the area of the special senses. One of her major accomplishments during this time was to plan a conference of national scope on Psychophysical Measurement in Chemosensory Research.

Jack Pearl, Ph.D., joined the Program as a Health Scientist Administrator in July 1980; his doctorate is in the area of experimental and physiological psychology (1964) and he additionally has a strong statistical and methodological background. Dr. Pearl's principal focus in the Program will be in the area of the special senses (taste, smell, touch and pain).

Rolf F. Ulvestad, M.D., has had respsonsibility for the past two years for the otolaryngological portion of the Program. He has served as a contract project officer and as a consultant and attending physician at the Clinical Center. His tenure with the Program terminated at the end of June 1980 as he returned to Minneapolis to enter private otolaryngological practice.

Mrs. Allison Grimes, Audiologist, has joined the staff of the Clinical Center Audiology Service in an effort to meet the steadily increasing call for patient audiological services.

Summer interns worked with Dr. Elkins this summer to develop materials for program conferences and to complete the proceedings of the workshop on the Effects of Noise on Hearing. All were under-graduate or graduate students in audiology.

J. Buckminster Ranney, Ph.D., Deputy Director of the Communicative Disorders Program, has served as Acting Director through June 1980 when Dr. Naunton took up his position as Program Director.

Christy L. Ludlow, Ph.D., Speech Pathologist, directs the speech and language portions of the Program. In addition to her extramural activities, she maintains a clinical research program with the assistance of Ms. Celia Cardano, a full-time research speech pathologist.

Earleen Elkins, Ph.D., Audiologist, directs the hearing portion of the Program. Her major responsibilities lie in the areas of communicative aids, the effects of noise on hearing and the management of hearing disorders. She also supervises the Audiology Service of the Clinical Center and directs clinical research with the assistance of Ms. Anita Pikus, audiologist.

Space is now available for patient testing in the Clinical Center, obviating the previously frustrating requirement that staff accompany patients to and from Building 36 for testing. Recent adjustments in policy are precluding the further testing of experimental test subjects in Building 36; plans are being made to resume this type of test in the Clinical Center using, if necessary, newly-developed portable test equipment. The Program Director has recently provided informational advice bearing on the soon-to-be-selected Director of the Communicative Disorders Program in the Clinical Center.

Communicative Disorders Program Activities

Ad Hoc Advisory Committee Meetings

The Advisors have met on two occasions during the past year. Each of the following was present at one or both of those meetings:

Dr. Robert C. Bilger
University of Illinois

Dr. Norman Geschwind
Beth Israel Hospital

Dr. Katherine S. Harris
Graduate School of University
Center of the City University
of New York

Dr. Murray B. Sachs
Johns Hopkins School of Medicine

Dr. David Smith
University of Wyoming

Dr. James B. Snow
University of Pennsylvania
(Philadelphia)

Program staff also attended those meetings, together with a number of representatives from the National Institute of Neurological and Communicative Disorders and Stroke. The Advisors have provided direction to the Program concerning future areas of research, in particular identifying those needing special emphasis. They have also critically evaluated staff suggestions for new or special initiatives, approving of them or suggesting alternatives. The next meeting is scheduled for October 1980.

Program Staff Activities

One of the National Research Strategy goals was to develop an x-ray microbeam system for speech movement research in a shared national center for U.S. speech scientists. As a result of a Request for Applications bearing on this subject, a proposal was funded in July 1980 for a system to be located at the University of Wisconsin in Madison. The system will have a number of distinct advantages over the one previously developed in Japan. It will require several years in development but the complete center should be operational within four or five years. (Dr. Ludlow)

Another National Research Strategy goal was to encourage training of investigators in the speech and language sciences areas, where there is a critical shortage. A program announcement for individual postdoctoral fellowships in this area, issued in 1979, resulted in thirty written inquiries but only three supportable applications. The paucity of applications may, in part, be the result of the limited number of high quality research training environments available in the speech and language sciences field; future efforts will therefore be made to increase the number of suitable training programs in these fields. (Dr. Ludlow)

One of the most pressing goals of the National Research Strategy was determination of language functions organization and the capacities of the left and right hemispheres at different stages in development, childhood and in language disorders. An NINCDS Monograph No. 22 (The Neurological Bases of Language Disorders in Children: Methods and Directions for Research) was published this year and is available without charge to neuroscientists. It is hoped this will stimulate interest in appropriate studies. (Dr. Ludlow)

The efforts to improve information services for specialists in communicative disorders have been significant this year. The MEDLINE Users Manual and Thesaurus for Specialists in Communicative Disorders (B. Reiner and C. Ludlow) was published in November 1979 and has been distributed to over 1,000 MEDLINE online centers and at various professional meetings. This manual provides scientists and other users with instructions on how best to use MEDLINE for searching the literature. (Dr. Ludlow and Dr. Reiner)

A display booth illustrating the value of MEDLINE has been designed and was used at four professional meetings during the past year. The display proved to be extremely effective and the Program was asked to use the display again at The 18th Congress of the International Association of Logopedics and Phoniatrics in Washington, D.C. in August 1980. (Dr. Ludlow)

Workshops were conducted by Drs. Ludlow and Reiner to instruct potential users of MEDLINE procedures. These were held at major scientific meetings. A pamphlet entitled, "Using MEDLINE for Literature Retrieval in Communicative Sciences" was published and distributed to the memberships of a number of professional societies. (Dr. Ludlow and Dr. Reiner)

An evaluation project was initiated this year to determine the effectiveness of MEDLINE services. Funding was approved by DHHS, and an RFP-NIH-NINCDS-80-09 entitled, "Evaluate the Effectiveness of Information Services Provided to Specialists in Communicative Disorders by MEDLINE" was released. Consequently, five specialized online centers to serve communicative disorders specialists have been set-up. User needs and the adequacy of MEDLINE services will be studied over a two and one-half year period. (Dr. Ludlow and Dr. Reiner)

A conference has been conducted on the subject of Acoustic Signal Processing, with special emphasis on the role of microprocessors in circuitry adaptable for amplification devices for the hearing impaired. The contributors represented expertise in electrical engineering, mathematics, experimental psychology, computer science, auditory physiology, speech perception and the rehabilitation of the hearing impaired. The results of this conference will be transferred into a Request for Proposal to develop a "bench model" which incorporates the innovative approaches for signal processing emerging from the conference. (Dr. Elkins)

The proceedings of the Program-sponsored workshop on "The Effects of Noise on Hearing" which was held in June 1978, have been edited and are being published as a monograph by the Institute. (Dr. Elkins)

The Program assisted in the planning of an international symposium on Menieres Disease, held in Dusseldorf (Germany) in May 1980. This conference was supported in part by the National Institute of Neurological and Communicative Disorders and Stroke. Dr. Ulvestad attended the conference as the representative of the Program. (Dr. Ulvestad)

In collaboration with the Office of Scientific and Health Reports a brochure entitled "Aphasia: Hope Through Research" has been developed. Work has started on the production of a similar pamphlet on stuttering. (Dr. Ludlow)

Dr. Ludlow was interviewed by the Canadian Broadcasting Corporation in January for a national radio broadcast on research advances in stuttering and by CBS radio network for the program "Health, Science and You" (CBS News) on stuttering.

Staff Activities

The following scientific presentations have been made at National and International Meetings:

- Ludlow, C.L. "Some hypotheses concerning the neurological bases of impaired language development." Orton Society.
- Ludlow, C.L., Richards-Munn, B. and Cullison, B.L. "Drug effects on the communicative abilities of hyperactive and normal children." The American Speech-Language-Hearing Association.
- Cardano, C.B. and Polinsky, R.J. "Speech symptoms associated with early signs of Shy-Drager Syndrome." The American Speech-Language-Hearing Association.
- Ludlow, C.L, Caine, E., Cudahy, E. and Cardano, C. "Effects of neuropharmacological agents on auditory processing skills in young adults." The Acoustical Society of America.
- Ludlow, C.L., Coulter, D. and Cardano, C. "Application of pitch perturbation measures to the assessment of hoarseness in Parkinson's disease." The Acoustical Society of America.
- Coulter, D., Ludlow, C. and Gentges, F. "Determination of lower limits of pitch variation in normal larynges." The Acoustical Society of America.
- Ludlow, C.L., Hanson, D.G., Williams, A., Cardano, C.B. and Coulter, D. "Laryngeal involvement in Shy-Drager syndrome." The Association for Research in Otolaryngology.
- Ludlow, C.L., Cardano, C.B., Brown, G.L. and Cudahy, E. "Effects of dextroamphetamine on auditory perceptual skills in hyperactive boys." The International Neuropsychological Society.
- Dr. Naunton presented a Short Course on "Presbycusis" at the Annual Meeting of the American Academy of Otolaryngology.

Presentations at Other Meetings

- Ludlow, C.L. "Role of Project Officers in Research Contracting" at GBA-NIH Seminar on the Contract Award Process.
- Ludlow, C.L. "Program and Project Planning" at the STEP module "Introduction to Extramural Programs of the NIH."

Other Professional Activities

Dr. Elkins served on two committees of the American National Standards Institute, completing a draft of a standard for spondee thresholds and working on standards for speech recognition testing and the determination of speech interference levels. She serves on the National Aeronautics and Space Administrations Executive Review Committee on Devices for the Hearing Impaired, as a member of the Federal Panel for Research on the Effects of Noise. She represents the Communicative Disorders Program on CHABA (Committee on Hearing, Bioacoustics, and Biomechanics), and has been appointed to a Working Group of CHABA, addressing the problem of tinnitus and tinnitus maskers.

Dr. Elkins served as Consultant in Audiology to the National Center for Health Statistics in the conduct of the National Health and Nutrition Survey for the Department of Health and Human Services.

Dr. Elkins has also served as a reviewer for the American Speech-Language-Hearing Foundation/Psi Iota Xi Sorority Research Awards.

Dr. Ludlow served as Chairman of the Committee on Scientific Affairs of the American Speech-Language-Hearing Association and as Liason Representative of the American Speech-Language-Hearing Association to the American Association for the Advancement of Science. She was editorial consultant for the following journals: Journal of Autism and Developmental Disorders; Journal of Speech and Hearing Disorders; Journal of Speech and Hearing Research; and Asha (American Speech-Language-Hearing Association).

Staff Publications

Hanson, D.C., Ulvestad, R.F., Ranney, J.B. Improving Grant Applications For Research in Communicative Disorders. Annals of Otol. Rhinol. Laryngol., 89: 257-261, 1980.

Ludlow, C.L. Children's Language Disorders: Recent Research Advances. Annals of Neurology, Vol. 7(6): 497-507, 1980.

Ludlow, C.L., Rapoport, J.L., Bassich, C. and Mikkelsen, E.J. Differential effects of dextroamphetamine on language performance in hyperactive and normal boys. In R.M. Knights and D.J. Bakker (Eds.), Treatment of Hyperactive and Learning Disordered Children: Current Research. Baltimore: University Park Press, 1980.

Ludlow, C.L. and Doran-Quine, M.E., Eds. 'The Neurological Bases of Language Disorders in Children: Methods and Directions for Research. NINCDS Monograph, Washington, D.C.: Government Printing Office, 1980.

Ludlow, C.L. Research directions and needs concerning the neurological bases of language disorders in children. In C.L. Ludlow and M.E. Doran-Quine (Eds.), The Neurological Bases of Language Disorders in Children: Methods and Directions for Research. NINCDS Monograph, Washington, D.C.: Government Printing Office, 1980.

Polinsky, R.J., Ebert, M.H., Caine, E.D., Ludlow, C.L. and Bassich, C.J. Cholinergic treatment in the Tourette syndrome. The New England Journal of Medicine, Vol. 302(23): 1310, 1980.

Reiner, B.J. and Ludlow, C.L. MEDLINE Users Manual and Thesaurus for Specialists in the Communicative Disorders. NIH Publication No. 79-1997, Government Printing Office, Washington, D.C.: 1979.

Elkins, E. (Ed.) The Effects of Noise on Hearing: Research Needs and Methodology. NINCDS Monograph, Washington, D.C.: Government Printing Office (in press).

Elkins, E. Summary of noise research needs and methodology. In Elkins, E. (Ed.) The Effects of Noise on Hearing: Research Needs and Methodology. NINCDS Monograph, Washington, D.C.: Government Printing Office (in press).

Ludlow, C.L. Recovery and rehabilitation in adult aphasic patients: relevant research advances. In R.W. Reiber (Ed.), Communication Disorders. New York: Plenum Publishers, Inc., 1980, in press.

Ludlow, C.L. Impaired language development: Hypotheses for research. Bulletin of the Orton Society, Volume 30, September 1980, in press.

Ludlow, C. and Bassich, C. The differential diagnosis of syndromes of dysarthria using acoustic measures. In Lass, N. (Ed.), Speech and Language: Research and Theory, Volume 5, New York, Academic Press, Inc., 1981, in press.

Ludlow, C.L. and Hart, M.O. Eds. The assessment of vocal pathology. ASHA Report, 1981, in press.

Ludlow, C.L. Directions for the development of improved methods for assessing vocal pathology. In C.L. Ludlow and M.O. Hart (Eds.) The assessment of vocal pathology. ASHA Report, 1981, in press.

Rappaport, J.L., Buchsbaum, M.S., Weingartner, H., Zahn, T., Ludlow, C., Mikkelsen, E., Langer, D., Bunney, W.E. Dextroamphetamine: Cognitive and behavioral effects in normal and hyperactive children and normal adults. Archives of General Psychiatry, in press.

Clinical Activities

Clinical speech and language research has continued under the direction of Dr. Ludlow with the assistance of Ms. Celia Cardano and in collaboration with intramural scientists in NINCDS and the National Institute of Mental Health. The goals of this program are:

1) to determine the effects of neurological diseases and disorders on speech and language functioning with the aim of identifying the specific speech motor impairments associated with pathologies affecting particular regions of the CNS; and 2) to study the effects of various neurochemical agents on speech and language functioning, in both normalcy and disease, with the aim of identifying effective treatments for such disorders.

During the last three years, a modest laboratory capable of supporting acoustic and some physiological studies of speech and language functioning has been developed and become sufficiently operational to support several research studies.

Highlights of accomplishments of this program this year include:

a) the development of a new method for assessing pitch perturbation in vocal signals which is stable across individuals regardless of differences in fundamental frequency. This method has a resolution eight times better than previous methods;

b) the finding that auditory processing deficits similar to those that occur in language impaired populations also occur in groups of patients who are without language, speech or reading disorders. This finding brings into question the assumption that auditory processing deficits are the basis for, or contribute to, the language disorders of language impaired populations;

c) the finding that the stimulants caffeine and dextroamphetamine, have different effects on speech and language in normal adults. Caffeine administration resulted in increased speech rate and rate of naming while dextroamphetamine increased speech fluency, the amount which subjects talk, but did not alter their speech rate.

d) the development of a set of 12 objective acoustic measures of speech timing and coordination was completed. These measures differentiate between different forms of dysarthria including hypokinesia in Parkinson's disease, Shy Drager Syndrome, buccofacial tardive dyskinesia, and Huntington's chorea. Discriminant functions incorporating these measures correctly identify the type of dysarthria degree of speech dysfunction. Such measurement tools provide the first set of objective clinical procedures for determining patients degree and type of speech dysfunction in dysarthria.

Dr. Elkins continues to participate in a study evaluating patients with neurofibromatosis and their families. Specialists in genetics and genetic couseling, neurology, neurosurgery, orthopedics, physical medicine and rehabilitation, otolaryngology, dermatology, radiology and cancer are cooperating to develop recommendations for treatment. Measures of evoked potentials to acoustic stimuli are an integral part of the evaluation procedures, identifying abnormal amplitudes and latencies in Waves I, II and III in a number of these patients. It appears that bilateral acoustic neuromas may be a hallmark of the central form of neurofibromatosis.

Dr. Ulvestad continued to provide teaching and consultative services in Otolaryngology at the Clinical Research Center and strengthened the clinical liaison with the National Naval Medical Center. He was appointed Assistant Professor of Surgery at the Uniformed Services University of the Health Sciences.

Dr. Ulvestad continued to provide otological and laryngological evaluation and assistance in three ongoing clinical research protocols: I. The NINCDS-sponsored study of neurofibromatosis, II) the study of audiological/otological findings in osteogenesis imperfecta, and III) the continuing assessment of vocal/laryngeal function and pathology.

Hearing (Function)

The performance of two types of cochlear hair cell are being studied to determine interactions between them and the roles of receptor potentials generated by them. The work includes recordings from single cochlear hair cells, studies of distortion effects in cochlear potentials, collecting single-unit data from fibers of the auditory nerve, and utilizing techniques of behavioral audiometry in animals. Major efforts were necessary to assemble the experimental apparatus for single hair cell recording and in experimenting with the production of various types of hyperfine microelectrodes. Three-week's effort yielded one identified outer hair cell, giving a total of seven positively identified outer hair cells from which recordings have been obtained. The difficulties in obtaining stable electrical recordings from outer hair cells and then identifying them histologically are formidable.

Studies on two-tone suppression and $2f_1-f_2$ generation in abnormal cochleas have continued. Nerve fibers with approximately normal tuning curves whose characteristic frequencies are just below a lesion caused by the destruction of outer hair cells were studied in detail. Results indicate that the extent of the resulting high frequency suppression is a function of the frequency separation between the border of the lesion and the best frequency of the fiber. When the separation is very small, the suppression area disappears. Likewise, if a fiber is within the lesion then it never shows two-tone suppression. In an effort to generate pure outer hair cell damage ototoxic agents other than kanamycin have been tried. A combination of bumetanide and kanamycin appears to give cleaner and more rapidly achievable lesions. A second line of research concentrated on the study of the dynamic response characteristics of primary fibers. Discharge patterns to brief high-frequency tone bursts were studied in the presence of low-frequency sinusoids.

In another research project, transduction and amplification of acoustic energy in the inner ear was studied, with particular emphasis on neural excitation of the auditory nerve fibers. Several projects have been carried out to determine the relationship between the electrical currents through the organ of Corti (as estimated from measurements of cochlear potentials) and auditory nerve (both single fiber and whole nerve) activity. Instrumentation to pass and monitor current between the scalae media and tympani was designed, constructed and used in experiments on the effects of electrically-induced endocochlear potential (EP) changes on CM and N_1. Experimental data have also been obtained from single fibers in response to low frequency acoustic stimuli. A substantial amount of time was devoted to the development of techniques to stimulate the cochlea electrically and to monitor the resulting electrical changes; the resulting system has been used in whole nerve and single fiber experiments. In order to eludidate the role of EP in neural excitation, the effects of slow variations of the EP upon the cochlear microphonics (CM) and whole nerve responses (N_1) to tone bursts are being studied in the guinea pig. The EP variations are produced by high intensity 50 Hz tones or by passing 50 Hz sinuoidal currents between electrodes inserted in the scala media and scala tympani of the first turn. The results indicate the N_1 response characteristics are not related simply to the AEPV induced by low frequency stimuli. Since the AEPV are produced mainly by the outer hair cells and the N_1 responses are produced by nerve fibers which innervate mainly the inner hair cells, the findings emphasize the need for more data so that functional roles of the two sets of hair cells may be determined.

Another research project sought an understanding of the way the auditory system extracts and encodes the invariant features of species-specific vocal signals, other sounds of biological significance, and sound localization cues, thus providing an understanding of the neural bases for sound communication. This work focuses on non-mammalian species; insights gained into animal communication and neural encoding in the auditory systems of simpler vertebrates, will lead to an understanding of the evolution and function of the auditory systems of higher mammals. During the mating season many species of anurans chorus for extended periods of time at high sound levels (100-120 dB SPL) generally most intense in the frequency range to which each species is most sensitive. In order to determine whether the exposure to these very intense sounds damages the frog's hearing, a systematic investigation of the effects of high intensity impulse noise on auditory thresholds in the green treefrog was undertaken. In a series of initial experiments, adult treefrogs were exposed to a prolonged series of high intensity clicks (167 dB SPL) having maximum energy within their most sensitive region of hearing (100-500 Hz). Within two months after exposure, neural thresholds were determined by recording multi-unit activity in the midbrain; no loss in sensitivity was found.

Morphological studies were carried out on animal and human inner ears in order to advance current knowledge on the peripheral auditory nervous system and the pathology of Menieres disease. Human spiral ganglion cells, in 17 ears from 12 individuals, aged 9 months to 92 years, were examined under the transmission electron microscope. There were two types of neurons, large and small, each with distinct cytological characteristics. Both types of neurons were myelinated and unmyelinated; however, a majority of the population was unmyelinated. A random sampling among the specimens showed great variation in the distribution of myelinated neurons, the highest count being 28% in the cochlea from a 72 year old individual. The small neurons constituted about 6% of the population, and their cytoplasms were highly filamentous in both myelinated and unmyelinated types. Nerve fiber synapses were observed on both types of small neurons. These and other observations conform in some respects with the concept of autonomic nerve fibers and neurons. However, these neurons may have an auditory function influenced by the synaptic contact of efferent fibers from the olivocochlear bundle. The surface structures of the membranous labyrinths in normal and hydropic inner ears from 28 guinea pigs were studied by scanning and transmission electron microscopy. In normal specimens differences between Reissner's and saccular membranes were observed. The endolymphatic epithelial cells of the saccule were smaller in size and their microvilli varied more in size and distribution. Mesothelial cells of the saccule were often spherical in shape and bulged toward the vestibule. In hydropic guinea pig inner ears, distension of Reissner's and saccular membranes occurred by irregular enlargement of epithelial cells, not by cell multiplication. In the severely distended Reissner's membrane, outpouchings, infoldings and holes were observed. The tight junctions of the distended epithelial cells did not differ from those of normal specimens. Mesothelial cells of Reissner's membrane were degenerated over a wide area of the cochlear apex; however, the saccular mesothelial cells were little affected in spite of the more severe distension. Cochlear sensory cells were often atrophic in the apical turn, but saccular sensory cells showed very little change in their surface structures. The ductus reuniens was successfully obliterated in 52 guinea pig ears. Histopathological study showed that a majority of these specimens demonstrated hydrops in the cochlea, collapsed saccule, and normal utricle. These results support the theory of longitudinal flow of endolymph from the cochlea toward the endolymphatic sac via the ductus reuniens and saccule.

Another study deals with the response of various structures in the middle ear to sound stimulation at the tympanic membrane. This is to be carried out under normal and pathological conditions in cadaver temporal bones by means of instrumentation yet to be developed and refined. This will employ the principle of laser interferometry in measuring the minute displacements involved in the hearing process. This technique allows attention to be focussed on small areas in the hearing chain, thus determining the contributions of small elements in the system without the imposition of nonphysiological constraints. The response to a wide frequency range (the entire audio spectrum) will be studied. Miniaturization of the optical instrumentation is the final step. Pathological variations (e.g., ossicular disruption, dysbarism, otosclerosis, and secretory otitis media) cause alterations in the normal vibratory pattern of the middle ear; the final intent is to determine the characteristic alteration in vibratory pattern produced by each of these pathologies so that they may be recognized from changes in vibratory pattern.

The objective of another study was to elucidate the molecular mechanisms of aminoglycoside-induced permanent hearing loss and to test the value of an in-vitro system employed as an indicator of drug ototoxicity. Perfusion of the perilymphatic spaces of the guinea pig cochlea provides a means of assessing the effect of aminoglycosides on cochlear microphonic potentials. The quality of the drug as well as the duration of exposure to the drug is under direct experimental control. The effects of various aminoglycosides on the cochlear microphonic potential were determined in this manner. Kanamycin B and Neomycin B were the most toxic, followed by Gentamicin C 1a, Ribostamicin and Kanamycin A; neamine and methylbiosamine, molecular fragments of neomycin, were not significantly toxic. The same drugs were analyzed for their ability to expand monomolecular films of polyphosphoinositides. The rank-order of effectiveness of the drugs was Neomycin B, Kanamycin B, Gentamicin C 1a, Ribostamicin, Kanamycin, Neamine and Methylneobiosamine. Except for the two most toxic drugs, there was a good quantitative relation between the in vivo toxicity and the in vitro action. The clinical significance of this work is that, if the molecular mechanism of ototoxicity is known, then those sites on the antibiotic molecule that are responsible for toxicity can be determined. Such knowledge would provide a rational basis for chemical modification of existing antibiotics to render them less ototoxic while retaining their antibacterial properties.

The goals of another project are elucidation of the factors involved in the development and maintenance of middle and external ear tissues in mammals. Reptilian, avian and mammalian systems are studied from three different vantage points: (1) anatomical analyses of normal and genetic mutant systems; (2) experimental manipulation of developing systems and (3) analysis of the post-trauma effects of experimental tympanic wounding. Choice of appropriate animal models for study of any problem with clinical implications demands careful analysis of the degree of similarity between the system of choice and human material. A pattern of cytological events in the chondrocytes of the avian fenestra ovalis region suggests a unique sequence of interactions in the formation of the columellar footplate significantly different from that seen in mammals. Analysis of an extensive series of reptilian embryos (lizards, snakes and turtles) has confirmed preliminary reports that they resemble the mammalian more than the avian condition. Previous descriptions of the development of the "meatal plate", the primordium of the external auditory meatus, as an "ectodermal invagination" seem to be incorrect. Further studies of mouse embryos have confirmed that the "plate" is nothing more than two epidermal surfaces opposed to one another by the increased mass of the dorsal and ventral mesenchymal tissues, aided by the ventro-lateral expansion of the neurocranium. Over 50 genes affecting the development of the mouse middle ear have been described. However since few accounts even mention the external or middle ear, it is impossible to assess whether or not these regions were affected. A major feature of this work is the identification of mutant strains whose tissues can be experimentally manipulated.

The neural regions involved in audition and vocalization in the Tokay gecko have been studied using experimental neuroanatomical techniques, to elucidate possible sites of interaction between these sensory and motor pathways and to gain insights into the organization of the neural pathways of audition and vocalization into a neural system which subserves auditory communication. The motoneurons which innervate the larynx are located in the nucleus ambiguous of the caudal myelencephalon. The current project is an investigation of the vocalization and auditory pathways on a single species. These studies will not only identify the sites and connections of the two pathways but will also provide an opportunity to identify sites at which interactions between the two pathways may occur. No previous study has adopted this unified approach to auditory and vocalization as the sensory and motor components of the larger system which underlies auditory communication.

The effects of acoustic trauma on degeneration of spinal ganglion cells have been studied in the cat and chinchilla. There appears to be a differential effect on the types of cells studied. In the cochlear nuclei of the cat and chinchilla different patterns of cochlear nerve degeneration are observed depending on the pattern of hair cell loss following acoustic trauma. These findings indicate different functional relationships between inner and outer hair cells and between the ventral and dorsal cochlear nuclei. Since these relationships depend on different groups of nerve endings it is possible that they are mediated by different populations of ganglion cells. The fine structure of cochlear nerve endings in the cochlear nucleus, labelled by injections of horseradish peroxidase, continue to be studied.

The purpose of another research program was to evaluate the functional role of the auditory thalamo-cortical system in hearing behavior. Intensity encoding has been studied in normal and pathological (noise-exposed) ears. Cells from the cochlear nucleus have been recorded under conditions of performance and non-performance. On the basis of online observations it appears in general that the changes seen at this level are consistent with those seen at other levels of the system (e.g., evoked responsiveness is greater under performance conditions). With complete analysis of the data it should be possible to report the effects of performance on cells of the cochlear nucleus. Analysis has been completed concerning the effects of inter-modality "attention" changes on evoked responsiveness in cortical cells. In this behavioral paradigm, under conditions of a stable stimulation environment, including pseudo-random presentation of auditory and visual stimuli, the monkeys were required to behaviorally respond (selectively "attend") to either the auditory or visual stimulus. Neural response to the auditory stimulus was measured under the two behavioral conditions. The differences in evoked responsiveness found with this behavioral manipulation were smaller than those seen with sleep/waking-state changes in which it was not uncommon to see vigorously responsive cells show marked reductions in response pattern. Similarly, changes in performance versus non-performance in a simple auditory behavioral task tend to yield somewhat greater changes in units' responses than seen in this investigation. Four monkeys have been studied in the past year in a noise study, primary efforts being directed toward behavioral analysis of the effects of short-term, high intensity exposure of low-, middle-, and high frequency tones on threshold and loudness-growth functions and the recovery of these functions following exposure. In addition, a few units have been recorded in the inferior colliculus peri-noise exposure. Required behavioral analysis is nearing completion. In addition, observations of changes in the CNS projections following noise exposure have been made in one monkey and three guinea pigs using autoradiographic axonal tracing techniques. Initial observations with this technique and associated procedures (horseradish peroxidase and dyoxyglucose) look promising.

In a study of the intracellular electrical activity of single cochlear hair cells, the cochlea of an anesthetized guinea pig was prepared by opening the scala vestibuli of the first turn, allowing for visual positioning of a procion-blue dye-filled electrode. The electrode was driven into the organ of Corti using a hydraulic microdrive. When a cell was successfully impaled, a series of acoustic tone bursts was delivered to the drum membrane. Each successive tone burst was stepped in frequency by 1 kHz starting with a base frequency of 10 kHz. The dc receptor potential (SP) for each burst of the series was recorded. The procion dye was then iontophoresed into the cell for marking purposes. Inner and outer hair cells within the cochlea of the anesthetized guinea pig have been successfully recorded. In the case of the inner hair cells, the cells have been held viable for a long enough period to allow the collection of frequency response curves (FRC's for up to 4 different iso-intensity sound levels). In the case of the outer hair cells two very short-lived cells were observed but not for long enough time periods to permit a single sweep of 15 frequencies. The primary observation from the two cells (one of which was dyed and histologically identified) was that they had a large intracellular SP just as did the inner hair cells. The significance of these findings is related to the future promise of the study. Preliminary data suggest that better quality and longer, more stable recordings from inner hair cells will be possible, and that outer hair cell data also can be obtained. Work on kanamycin-intoxicated cells will begin to provide knowledge about individual sensory cells of the ear--the cells which ultimately suffer dysfunction and/or death in sensorineural hearing disorders.

The ontogeny of structural and functional relationships in the development of auditory information processing has been examined. This study made use of an explanted in vitro brain stem preparation, allowing electrical stimulation of the eighth nerve and microelectrode recordings of post-synaptic potentials (unitary spikes) in n. magnocellularis and n. laminaris. Through dye marking the age and the spacial-temporal organization of functional synaptogenesis in these nuclei was determined. The principal findings were: 1) synaptic transmission begins in the rostromedial portions of both nuclei on embryonic day 11; and 2) there is a spacial-temporal gradient of synaptogenesis from rostral-medial to caudal-lateral over the period from embryonic days 11 through 14. The first result is important since it provides the first concrete data relating normal embryonic cell death to synaptic development. Otocyst removal does not influence cellular development until after embryonic day 11 and in an earlier examination of normal ontogeny, embronic cell death is maximal during the embryonic period between days 11 and 13 of embryogenesis. The second result further supports the observation of spacial gradient of development in central auditory structures which matches that of the cochlea (basal to apical) and is the opposite of the responses to sound. This finding, then, provides strong support for the theory suggesting a developmental change in cochlear transduction properties. Another series of studies deals with the ontogeny of auditory information processing. The capacities of the embryo to code auditory stimuli, and the topographic organization of frequency coding in the embryonic brain stem are examined. Eighth nerve potentials are being recorded from the round window to determine ontogenetic changes in thresholds and simultaneous masking tuning curves of the receptor. Preliminary results show delayed development of high frequency thresholds and ontogenetic "sharpening" of peripheral "tuning curves".

Auditory thresholds have been measured in several taxonomically distinct species that demonstrate significant modifications in their peripheral auditory systems that may affect hearing capabilities. Thresholds were determined in sound-proof rooms using standard operant conditioning techniques. Thresholds were measured for Notopterus chitala. Gnathonemus petersii and Hemichromis sp. Notopterus has swimbladder projections directly to the sacculus of the inner ear, a feature in the auditory system that should provide enhanced detection of sounds. However, behavioral results show that Notopterus hears no better than fishes which do not use the swimbladder in hearing. This species could detect sounds up to about 1,000 Hz with best sensitivity at 300-500 HZ (about -20 dB re: 1 microbar). In contrast, auditory thresholds for Gnathonemus, a species with a small air bubble by the ear, are extremely good, with best sensitivity from 400 to 1,000 Hz and hearing sensitivity that extends to over 2,500 Hz. The third species studied, Hemichromis, has no swimbladder modifications and initial data show poor hearing sensitivity (+10dB) at

500 Hz, with little or no auditory sensitivity above about 900 Hz. In addition to measures of hearing sensitivity, studies of the analysis mechanisms of the ear through use of psychophysical tuning curves have been completed. Studies have been conducted with Notopterus using both simultaneous and forward masking paradigms; there are some differences in the psychophysical tuning curves obtained with the two methods (similar results have been found in mammals) and there are distinct peaks, the sharpness of which (at 300 and 500 Hz) suggest reasonably good tuning in the auditory system of this species. Significantly, the data for Notopterus differs somewhat from that obtained for Adioryn, a species that has no connection between swimbladder and the inner erar. These and other data suggest that several different types of analysis mechanism may be found in the teleost auditory system. These data demonstrate good frequency discrimination, at least in some species. Investigations of the ultrastructure and gross morphology of the ear have been conducted using the same species for behavioral and anatomical studies. In Notopterus the "abberant" auditory sensitivity functions may be related to particular aspects of the anatomy and ultrastructure of the inner ear, particularly as related to the structure of the swimbladder and the ear. Preliminary evidence indicates that different regions of the sensory macula of the ear are responding to different components of the acoustic signal.

In an electron microscope study of the synaptic organization of the avian brain stem auditory center nucleus magnocellularis (NM) and nucleus laminaris (NL), synapses in both nuclei have been classified according to quantitative morphological criteria and by the use of ultrastructural localization of acetylcholinesterase. The cells of origin of the principle synaptic types in NM and NL (viz. the cochlear nerve and NM, respectively) have been identified by labelling the terminals with horseradish peroxidase. The otocyst (the embryonic precursor of the inner ear and cochlear ganglion) has been surgically removed unilaterally in a substantial number of animals and large age-graded series of brains have been prepared by the rapid Golgi, Golgi-Kopsch, and electron microscopic methods. Although the detailed analysis of this material is just beginning, it is clear that the normal dramatic sequence of structural transformation in NM is altered and that there is a marked change in the shape of NL dendrite following this early deafferentation. A large number of embryos from seven days of incubation through hatching have been prepared by the same methods for a study of the normal morphological development of NM and NL. A study designed to assess the effects of early profound unilateral conductive hearing loss on brain development is proceeding. The dorsal wings of the first and second Pharyngeal pouches are surgically removed in five-day chick embryos and the animals are allowed to develop until days 15-18 of incubation. Analysis of Nissl-stained material indicates that this procedure results in a severely malformed middle ear without producing marked damage to the inner ear; this will permit the desired analysis of the effects of a "pure" conductive hearing loss on brain development.

Work in the areas of lateral suppression and psychophysical tuning curves yielded unexpected results. Studies show that the psychophysical tuning curves of subjects with sharp high-frequency hearing loss are atypical in a number of ways. Theoretically, similar effects could be produced in normal listeners by introducing a high-pass masking noise to simulate the loss of sensitivity of the hearing-impaired listeners. Psychophysical tuning curves (PTC's) were then measured under these conditions at a number of signal frequencies both in the presence and the absence of high-pass noise. To simulate a moderate hearing loss, the spectrum level of the noise was only about 35 dB SPL (overall level about 65 dB). The data collection process was counterbalanced, so that within and across daily sessions the three subjects were "exposed" intermittently to the noise band in segments of about four minutes separated by breaks of at least one minute (and sometimes many minutes while no-noise conditions were being run). The expected effect was emerging --the PTC's were different in the expected ways with the noise present--but as the experiment proceeded it became clear that something strange had happened to the data in the no-noise conditions. To be specific, there was a loss of tuning in the non-noise PTC's of two of the the three subjects. The remaining scheduled "exposures" to the noise band were cancelled, and the subjects' PTC's were repeatedly measured over a period of months. There was for both subjects some recovery toward the pre- "exposure" PTC's, but even after several months recovery was not complete. Because the noise band was so weak, the temporary and permanent aspects of this previously undiscovered auditory after effect are due to the unusually steep spectral slope of the noise band. A second belief is that the PTC is a particularly sensitive tool for detecting this after effect. Such standard measures as absolute threshold and frequency discrimination indicate no change post-"exposure". One of the two affected subjects showed diminished lateral suppression post-"exposure", however. Studies of the loss of tuning following "exposure" to steep-sided noise bands will be continued. All subjects are given full explanations of the effect as presently known and of the precautions being taken. These include daily pre- and post-"exposure" measures of the PTC and gradual increases of the "exposure" duration. If steep-sided noise bands do prove capable of producing short- and long-term changes in auditory acuity, there will be considerable real-world implication. The increasing use of microprocessors makes synthesis of desired waveforms more efficient and economical than processing conventionally generated analog waveforms into the desired configuration. Such synthesis obviously makes steep-sided waveforms more easily obtained than in the past and were they to creep into every day devices such as tinnitus maskers, talking dolls, music boxes, electrical musical instruments, audiometers, etc., a health problem might thereby be created.

The results obtained thus far on the ears of amphibians, and especially those of the most important order of anurans (the frogs and toads), has made more certain than before a position early suggested, that the amphibian ear does not lie on the line of evolution leading to the higher type of ear as found in reptiles, birds and mammals. Rather, this ear appears to be an independent development, a side branch of the evolutionary tree, with no counterpart elsewhere in the animal series. The evidence indicates that both amphibian and reptilian ears developed from ears of certain fishes, but along separate lines. This view runs contrary to long-accepted doctrine, but the evidence for it is growing as the research proceeds, and even now can be considered as overwhelming. This evidence arises in a consideration of structure and function both of inner and middle ear regions. A careful examination of these two parts of the sound receptive mechanism in amphibians and in higher vertebrates makes it almost certain that there are no true homologs; the same names are generally used for the structures, and can justified as designating analogous elements, but no more than this should be implied. The most significant difference is in the mode of stimulation of the hair cells, and is a difference so fundamental that it is almost inconceivable that one form of ear could be converted into the other by evolutionary processes. Physically these stimulation processes are just contrary to one another: in reptiles and higher vertebrates there is a basilar membrane that bears the hair cells on its surface which are moved up and down as the membrane vibrates in response to pressures exerted on the membrane through the inner ear fluid. At the same time the cilia of the hair cell are restrained by connection to a tectorial strand that is anchored to a side wall; hence there is a relative motion between cell body and ciliary tuft that stimulates the cell. In amphibians there is no basilar membrane; the hair cells lie on a solid base and their cell bodies do not move.

Subjective-harmonic amplitudes between ears, listeners, and frequencies are basic data relevant to several clinical and theoretical issues. Monaural tone-on-tone masking measurements for the second and third harmonics of 250, 500 and 100 Hz have been obtained at 75 dB SPL from subjects with normal bilateral hearing. The estimates of the corresponding aural harmonic amplitudes tend to: (1) be lower at the third than second harmonics; (2) differ nearly as much between ears as subjects; (3) correlate with overall masking levels across but not within frequencies, and (4) increase slightly with fundamental frequency. These latter two findings are particularly interesting: (3) because such a correlation implies a previously unsuspected non-independence of the distortion and masking processes, and (4) because such increases are inconsistent with the simple power-series description of aural distortion. Sensation level of the fundamental may mediate these increases in both masking and distortion. The amplitudes of inaudible subjective signals are estimated using the monaural tone-on-tone masking procedure. These inferences are based upon three major assumptions: phase-locked generation of subjective signals, vector summation between a subjective and acoustic tone, and the independence of the distortion from the sensitivity processes. Accordingly, any shift in sensitivity without an accompanying change in distortion levels should produce quantifiably predictable variations in the measured phase-amplitude effects. Since the assumptions would most likely be violated at low frequencies, this prediction has been tested with a 250-Hz masker, and comparisons of relatively long- vs short-duration thresholds for a 500-Hz maskee (probe). Observed decreases in phase-magnitude effects with increasing losses in sensitivity follow predictions. These findings: (1) support the validity of the estimation procedure among subjects with normal hearing, (2) suggest a control condition important in estimating subjective tones among abnormal-hearing subjects, and (3) have implications for inferring the origins of the monaural phase effects widely observed with inharmonic and harmonic probe tones of relatively high intensity.

In the goal to establish effective, reliable methods for measuring hearing aid performance, current research emphasizes the investigation of the reliability of speech recognition tests that can be used effectively on persons with sensorineural hearing loss. Computer strategies have been developed to digitize the speech and fully automate the psychoacoustic procedures for delivery and retrieval of the speech stimuli. Three major studies have been initiated and either completely or partially completed. An initial experiment was performed to determine whether speech discrimination performance improves above the loudness discomfort level (LDL) of sensorineural deafened listeners. Performance-intensity functions were measured on 30 subjects with sensorineural hearing loss. For both monosyllabic words and sentences (SPIN), speech recognition scores obtained at levels below the LDL were equivalent to or higher than scores obtained at and above the LDL. This result supports the contention that speech signals need not be amplified above the LDL for hearing aid users and provide further impetus for restricting the saturation output of hearing aids to levels below the subject's loudness discomfort level. In a second experiment, reliability of the closed set Nonsense Syllable Test was established on a large group of patients with sensorineural hearing loss. The estimates of reliability have been completed. The results demonstrate very high reliability for this test and have been used in a second experiment to determine the effects of three spectral shapes on response of each subject. The subjects for the experiment are 6 persons with sensorineural hearing loss with "flat" audiometric configurations and 6 individuals with steeply sloping losses. Besides the Nonsense Syllable Test, subjects are tested at several sound pressure levels with the Synthetic Sentence Identification test of Speaks and Jerger. Measurements of threshold and loudness discomfort level are also included using computer programmed adaptive procedures. Three experiments were also completed in the auditory masking portion of the program. In these, the detectability of tonal signals in computer-generated band-reject noise were investigated. In Experiment I, detectability of a 500, 1000 or 2000 Hz tone presented at 50 dB SPL was measured as a function of the width of a spectral "notch", symmetrically spaced around the tone. A narrow notch resulted in decreased detectability relative to the wide band (zero notch width) control condition. Further increases in notch width resulted in increased detectability until subjects approached errorless performance. In Experiment II, Psychometric functions were measured for a 1000 Hz tone presented in four notch noise conditions. The slopes of the psychometric functions were consistently steeper in the band-reject conditions relative to the zero notch width condition. These slope differences result in relationships between threshold and notch width that vary depending upon the region of the psychometric function from which the threshold estimates are obtained. In Experiment III, the decrease in performance associated with the notch was found to increase in proportion to notch depth. The data suggest that spectral edges placed in the immediate vicinity of a tone reduce the detectability of the tonal signal. This "edge effect" is discussed in relation to two-tone inhibition that has been observed in the auditory nerve.

Melodic interval recognition experiments using dichotic two-tone complexes of nonsuccessive harmonics have been completed. The results of this work indicate that the optimal processor and virtual pitch theories have very similar behavior, although their formulations are quite different. Behavior prediction by the pattern transformation theory is very different, especially for complexes of successive harmonics. The data show strong support for the former theories in contrast to the latter. At the same time, the data show strong evidence for an "analytic" pitch perception mode in which the pitch of a 2-tone complex is judged on the basis of the open-tone pitch of a (dominant) tone component. This mode is currently not incorporated in any of the pitch theories, although Terhardt's theory explicitly recognizes its existence.

Hearing (Disease)

An extensive test battery was revised. It now comprises an extensive sampling of prosodic, phoneme, word, and sentence recognition materials recorded on a master reel-to-reel tape. Cassette recordings dubbed from the master tape, along with response and scoring forms may be obtained by other investigators for the cost of dubbing. The revised battery has been administered to three cochlear implant patients including two who had also received the original battery. An earlier study, utilizing the original battery, had shown that profoundly impaired subjects with hearing aids performed consistently better than implant subjects, but that one implant subject consistently achieved better scores than two others. The implant subject with the best scores was unique among implant patients in that he could, without visual cues, recognize consistently about half of a series of 25 two-syllable words in an open set and about 40% of key words in the CID Everyday Sentences. The implant worn by this subject consisted of an 8-channel bipolar electrode array in the scala tympani with wires leading to a temporary percutaneous plug seated on the mastoid. Interface equipment was employed in testing various combinations of the 16 wires in order to determine those combinations providing the best understanding of speech and to plan the design of a wearable multichannel receiver-transmitter.

The efficacy of steroids in the treatment of idiopathic sudden hearing loss has been examined. The results of two separately administered double-blind clinical studies were combined. Drugs administered were Dexamethazone (Decadron) and Methylprednisolone (Medrol). While steroid dosages used by the two groups were different, the anti-inflammatory effect is thought to be equivalent. All subjects had experienced a hearing loss of at least 30 dB in 3 contiguous frequencies in less than three days, had received no prior treatment, and were seen within ten days of the onset of the hearing loss. Lab work was carried out in order to exclude treatable forms of hearing loss. Audiograms were obtained at intake, 4 weeks, and three months post onset of SHL. For the purposes of analysis, 3 types of audiograms were identified: mid-frequency losses, profound losses of 90 dB or more at all frequencies, and hearing losses falling in between these two extremes. A total of five groups were studied: 2 received placebos, 2 received steroids, and 1 received no treatment. The results of the studies showed the overall steroid recovery rate to be 61% and the overall placebo recovery rate to be 32% when the two steroid and two placebo groups were combined. The difference in these rates is significant. 100% of the patients with mid-frequency hearing losses had complete recovery regardless of treatment. The propensity for recovery in this group was recognized early in the study and most were not included in the double-blind medication trial. Only 14% of these subjects had experienced vertigo. No relationship was found between age and this or any other type of audiogram. Seventy-six percent of patients with profound hearing losses (90 dB or more) had no recovery, while only 24% experienced some recovery. The double-blind study could not demonstrate a beneficial effect of steroids among these patients. 79% of this group experienced vertigo. In general, the frequency of vertigo increased with the severity of the hearing loss. The chances for recovery increased 4 to 5 fold when steroids were used as opposed to placebo or control in the treatment of ISHL. By contrast, no difference in the recovery rates of the placebo and untreated control groups was found. If these groups are combined to form a single untreated control group and are compared with the steroid group significant differences in the recovery rates exist. The estimated relative odds favoring recovery in the steroid group is 4.39 to 1. Therefore, for those sudden hearing losses which are mid-frequency and severe, steroids have a definite positive effect upon recovery. The nature of this hearing loss, and its susceptability to improvement from steroids, lends support to the hypothesis that viral cochleitis is the primary cause of ISHL.

Secretory otitis media is characterized by the production and accumulation of mucous secretions which are an important factor in the etiology and treatment of the disease. An improved understanding of the role of the secretions and their physicochemical properties would be of significance in devising more rational treatment. The rheological (viscoelastic) properties of middle ear secretions from patients with secretory otitis media, with and without generalized respiratory disorders are studied and compared with their mucociliary transport and with certain chemical properties. Also, the physicochemical properties of samples from individual subjects will be correlated with their clinical status. Preliminary studies, have shown that there are differences in the rheology and transport of secretions from patients with secretory otitis media, with and without cleft palate.

The objectives of another study were to validate automated procedures for determining tonal thresholds using middle component AERs; to integrate the automated system into an on-line decision-making system for threshold audiometry; and to assess the applicability of this on-line system to actual clinical populations. 20 adults with sensory-neural hearing losses ranging from 21-72 dB nHL for the tone-pips of 500 and 2000 Hz have been tested. Averages of 1024 artifact-free sweeps were obtained at 8 intensity levels for each frequency. The responses were scored for threshold determination using the methods of criterion score and discriminant analysis based on models of responses from 30 normal-hearing subjects. The response waveforms were not significantly different from those for normal-hearing subjects at low sensation levels. That is, the composite across the group of hearing-impaired subjects did not differ from the composite of normal-hearing subjects. For all subjects, one or more of the scoring procedures was successful in identifying responses at or better than 30 dB SL. All scoring methods tended to fail more frequently on certain subjects. A visual inspection of those subjects' waveforms showed high levels of background "noise" which we believe is more of a problem for response scoring than actual changes in waveform configuration of the middle component response. Using 50 db HL clicks, ipsilateral and contralateral responses from 22 infants (4 to 35 weeks) have been collected. For all infants under 22 weeks old, the ipsilateral middle components are larger than the contralateral; for infants 22 weeks old or older, some infants show no significant sideness difference. Data from 2 patients with cerebral palsy and 18 aphasic patients with left temporal lobe lesions has been collected. For the patients with spastic cerebral palsy, automatic as well as visual scoring procedures failed because with the small number of sweeps (1024) set as a goal, muscle artifacts produced too much "noise" to identify a response consistently. A larger number of aphasics than originally proposed was studied. The initial impression is that the changes will not be so large as to invalidate all scoring procedures, particularly for responses recorded from the undamaged side of the head.

The question why mucus accumulates in the middle ear spaces in cases of Secretory Otitis Media is at the central theme of another investigation--a problem of mucus production and clearance. Evidence that it is possible and valid to make comparisons between mucociliary epithelia in general and pool all information so obtained has been determined. This approach makes it considerably easier to discuss the problem in the middle ear and Eustachian tube--difficult regions for direct experimentation. In addition to the well known basic frequency of ciliary beat, there is a very low frequency superimposed. This explains why ciliary activity is found to be sporadic. Cultures of excised tissue leads to the formation (growth) of a monolayer of cells with the original tissue sample in the center. The cells in the monolayer can differentiate and produce both mucous-secreting and ciliated cells. The cilia on these newly formed cells have a statistical preference to beat in one direction. The preferred direction is coordinated with the direction of beat on the original tissue. Cilia in the outgrowth tend to produce flow in a direction opposite to that of the original tissue sample.

The objectives of a study of sound-evoked potentials in infants included: (a) the development of a safe non-invasive measure of brainstem auditory function (BAEP) for the evaluation of term and pre-term infants, (b) the acquisition of normative data from infants between 28 weeks and term, (c) the determination of pathologic changes due to hyperbilirubinemia and birth hypoxia or respiratory distress syndrome by this method, (d) the assessment of the effects of phototherapy and exchange transfusion in hyperbilirubinemic infants on these responses, (e) the determination of the accuracy of this method compared with behavioral tests of development and conventional hearing tests in the nursery and followup. As the study of the pre-term infants proceeded it became evident that more complete normative BAEP and bilirubin data were needed for conceptual ages between 28 and 38 weeks. Modifications in selection of subjects have been made to obtain this data and data from infants with hyperbilirubinemia and hypoxia. It involves random study of pre-term infants upon admission to the intensive care nursery and at weekly intervals until discharged. This plan presumes that many of these infants will have an uncomplicated post-natal course and that other infants will develop hyperbilirubinemia or hypoxia or both. Thus, normative data will be obtained concurrently with studies of the at-risk population. The normality or abnormality of the pre-term infant will be determined at the time of discharge from the nursery and appropriate follow up arranged. A longitudinal study of these infants will be more sensitive in detecting dysfunction than one selecting infants after the problem becomes clinically apparent. Another modification of the BAEP procedure has become necessary for identification of components. Simultaneous recording of both ipsilateral and contralateral ear-to-vertex recordings are being obtained. The intensity of the stimulus has been standardized. Monaural data from both ears is essential to detection of peripheral and central auditory dysfunction. The bilirubin determinations have been expanded to include a test of free bilirubin albumin binding capacity whenever sufficient quantity of blood is obtained. This we expect will assess the predictive value of this procedure as well as yield additional correlation with clinical and electrophysiological data.

The histopathological findings in the temporal bones of a case of unilateral endolymphatic hydrops in a 67 year old male, completely unsuspected during life, included a blind venous loop formed by the venous branches draining the vestibule, with no vein present in the para-vestibular canaliculus. The saccule showed an old chronic rupture, which probably accounted for the absence of symptoms. There was very mild endolymphatic hydrops of the first part of the cochlear duct. This case raises the question of the significance of the venous drainage of the vestibule and/or vestibular organs, whether interference with venous drainage alone, might account for some cases of endolymphatic hydrops. This case was thought to represent congenital absence of the vein in the PVC. The marked congestion of the veins draining the vestibule area and congestion of the inferior cochlear vein suggest that a certain degree of collateral circulation through the inferior cochlear vein probably occurred.

A study has demonstrated the value of microdissection and surface preparations for the examination of temporal bones with capsular otosclerosis, and for defining the relation between otosclerotic foci, sensorineural degeneration or vascular changes. Otosclerotic foci were clearly seen and photographed during removal of the otic capsule, and the state of each focus, i.e. whether it was active (spongeotic), partly active, or inactive (sclerotic), could be judged on the basis of its consistency and its vascularity. In 24 temporal bones, each of which had an ankylosed stapes or had undergone stapedectomy, small anterior foci were most common. These foci did not appear to have caused any sensorineural degeneration. On the other hand, large anterior foci extending to the upper basal turn showed associated sensorineural degeneration. One specimen showed a circumscribed degeneration of Corti's organ and its nerve fibers in the upper basal turn, corresponding almost exactly in location and extent with the site of invasion by the otosclerotic process of the endosteum bordering on scala tympani and scala media. Since an anterior focus so commonly expands into the upper basal turn, this region may represent a site of predilection for sensorineural degeneration in capsular otosclerosis. An audiometric pattern with a low-frequency dip may be characteristic of this form of otosclerosis. Vascular shunts of capillary size were found in two specimens, and large shunts resembling those described by Ruedi and Spoendlin and associated with severe vasodilatation suggesting a distrubance of the local cochlear circulation, were present in three others. Atrophy of the stria vascularis and the spiral ligament was seen in cases with multiple foci, one of which also showed several holes in the basilar membrane. Sensorineural degeneration of the entire vestibular system had occurred in one specimen with multiple foci. The bones from two of the four patients who had undergone fenestration showed extensive and severe vestibular pathology. One stapedectomized patient had a fistula of the saccular duct, but degeneration of the macula sacculi was no greater than would be consistent with the patient's age. One patient with a history of vertigo showed severe hydrops in one labyrinth and mild hydrops in the other. There were multiple otosclerotic foci, but it was not clear that they had anything to do with the hydrops.

The objective of another study was to elucidate the mechanisms of injury in the inner ear which lead to impaired function or total degeneration of sensory and supporting cells, nerve fibers and the cells of the stria vascularis. In a sample of 150 chinchilla ears, the length of the organ of Corti was found to be normally distributed around a mean of 18.31 mm with a standard deviation of 0.89 mm. Measurements of cross-sectional area of the organ of Corti and width of the basilar membrane were made at 11 locations in five ears which ranged in length from 16.00 to 19.71 mm. The data from short, average and long ears were in good agreement when plotted as a function of percent distance in the cochlea rather than distance in millimeters. In long cochleae, the average density of inner and outer hair cells was approximately 12% less than that of short cochleae whereas the length was as much as 30% greater. This indicates that long cochleae have a greater number of sensory cells in a given frequency region. Radial sections of inner and outer hair cells were made at 11 locations in eight cochleae which ranged in length from 16.00 to 19.71 mm. These specimens were from non-exposed controls or from animals which had had minimal exposures at least 30 days prior to sacrifice.

Examination of 331 human temporal bones (226 cases aged 8-102 years) revealed the presence of a microfissure in the oval window area in 25%. It appears that a microfissure rarely occurs in this area before ten years of age but that it begins to be observed in individuals above age 10 with an incidence which increases sharply at about age 40. In 61% of the bones in which the microfissure was observed, it was present both above and below the oval window in almost the same vertical plane. The histological appearance of the microfissure in this area was quite similar to that of the microfissure between the posterior canal ampulla and round window niche. The histogenesis of the microfissure is still unknown; nontraumatic spontaneous fracture by mechanical stress is the most probable explanation.

Vestibular (Balance)

Study has been directed to the understanding of the human postural control system. The approach used has been to develop a platform which can be used to move a subject's base of support and a measurement system which records the response of the body to the induced instability. The movement of the platform is commanded by a digital control system and therefore has considerable inherent flexibility. To date, three classes of platform motion have been used to test human subjects: 1) Sine wave, 2) Step changes of position and 3) Pseudorandom low-pass noise. The current activities on the project involve the development of a quantification procedure for the reduction of the data to meaningful parameters and the building of a data base for male and female normal subjects with a variety of body types and ages. A data base of clinical cases which can be used to help dissect out the relation between the patterns of motion observed and related pathologies will be developed. At first this will be done by a pattern recognition approach but will later be supplemented by a system modeling approach.

The aim of another program of vestibular system research is to describe the operation of the peripheral vestibular end organs and the ways in which information encoded peripherally is modified in central pathways. The long range goal is an understanding of the functional contributions made by various components of the vestibular system. Specific goals were (a) to study the response of peripheral vestibular afferents to electrical stimulation; (b) to characterize the horizontal vestibulo-ocular reflex (VOR) in normal animals and after inactivation of a single horizontal semicircular canal; (c) to begin a study of the response of vestibular afferents to rotations about an earth-horizontal axis. A major result of the electrical-stimulation studies is that the regularity of discharge of an individual afferent is largely determined by the time course of postspike recovery in the afferent terminal. The most important conclusion of the VOR study is that, following canal inactivation, there is an adaptive gain change in the VOR which depends on visual-vestibular interactions. This last finding is of particular significance since it implies that adaptive gain changes, which had previously been evoked by optical means, can indeed compensate for pathological changes in the VOR pathway itself. The study of earth horizontal rotations is in a preliminary stage, but the tentative conclusion is that the prolonged nystagmus obtained with such rotations cannot be explained solely in terms of semicircular-canal mechanics.

Another vestibular system project was devised to determine whether or not a test that measures the patient's ability to control his posture can detect vestibular lesions. The study evaluated the relationship between body angle and force plate measurements. However, force plate measurements taken while the platform was moving in response to body sways were of doubtful validity, even though complicated transformations of these data were undertaken to correct for platform movement. Therefore a determination whether force plate data could be predicted by analysis of body angle measurements was undertaken. The analysis showed that the center of mass from body angle measurements could be estimated with remarkable accuracy. The analysis of these data is incomplete, but it suggests that the 95 percent confidence limits of the estimates are within 1-2 percent of measured values. This result indicates that force plate measurements may be estimated, thus simplifying the data collection procedure. The postural control responses of an additional group of normal subjects was analyzed using an improved two-camera system. This analysis confirmed some of the earlier conclusions and failed to support others. The one-link model of body sway motion (which assumes motion only at the ankle joint) was inadequate. Departures for the one-link model are related to the difficulty of the postural control task. When the task is an easy one, ankle joint movement predominates. When it is difficult, control is achieved by movements of other joints, especially the hip. The instability produced by denial of vision was minimal at all sway frequencies; instability caused by nulling ankle angle was marked, but not confined to high frequencies as indicated by previous data. The data also revealed a previously-unrecognized phenomenon: many subjects displayed large postural shifts at apparently random intervals during the trials. Under the method of data analysis, these shifts are interpreted as postural instability, but it is now apparent that they are not; rather it seems more likely that the point of postural stability is multi-valued.

The concern of another research project is the principles underlying the vestibulo-ocular reflexes. Response characteristics have been examined to allow the development of models of the functional connections between the receptor organs of the labyrinth (cristae and maculae), the neck proprioceptors and the oculomotor control system during production of nystagmus. Studies include: 1) Detailed analysis of the eye movements resulting from stimulation of individual receptor organs (semicircular canals, otoliths, neck proprioceptors, retina) and interaction of inputs to two or more of the above receptors; 2) Investigation of the physiological factors regulating the complete trajectory of the eye during nystagmus, especially those features of the stimulus and the eye movement which lead to the production of fast components for each of the individual reflexes; 3) Elucidation of the intrinsic mechanism of production of complex eye movements such as nystagmus through analysis of recordings of neural activity in the neurons and pathways of the vestibulo-ocular reflex arc; 4) Neural connections will be modified experimentally and correlations made between the changes in single neuron activity and in the resulting reflexive movements; 5) Comparisons of change in ocular response, predicted by suitable models of the vestibulo-oculomotor system, which we are developing and testing, with observed changes in ocular response induced by physiological or surgical procedures that stimulate known pathological states of the vestibulo-oculomotor system; 6) Investigation of optimal stimulus conditions and of parameters of eye movements which enhance the probability of identifying vestibulo-oculomotor disorders. Measurements were made of the responses characteristic of single abducens fibers in cats. The results of the study are consistent with the hypothesis that the changes in motorneuron firing for all types of eye movements are linearly related to both eye position and velocity. During vestibular nystagmus their change in frequency of firing exhibits the same mathematical relationship to the change in the eye position independent of the type of eye movement, agonist or antagonist. Time constants of the velocity to the amplitude of the eye motion, were found to be the same in cats as in primates.

Another study concerns the vestibular system control of eye and head movements in health and disease. In acute cats the major functional classes of reticular formation neurons and their firing patterns have been studied in relation to nystagmus. The nystagmus has been produced by rotation of a turntable, or by electrical stimulation of one or the other labyrinth, or by labyrinth destruction on one side. Single neurons were recorded extracellularly in the reticular formation. Compound action potentials of the abducens nerve or of the medial rectus branch of the third nerve were recorded. The main timing point used was the termination of slow phase discharge of one or another of the eye nerves. Discharge patterns of the brain stem reticular formation neurons were related to this. Fast green FCF dye spots identified 1 to 3 neurons per cat and the histological location of other neurons was determined by measurements made during the course of the experiment. Classes of neurons thus recorded included medium lead burst neurons, pause neurons, burst inhibitory neurons, burst tonic neurons and a few other less-frequently observed types. Based on the different functional behavior and different histological locations, these separate groups of neurons were then analyzed for the role which they play in eye movement.

Studies have been carried out to identify the transmitter substances involved in several defined vestibular pathways. For this purpose, comprehensive systematic studies of the distribution of the four putative amino acid transmitters (gamma aminobutyric acid (GABA), glycine, aspartate, and glutamate) were undertaken. GABA and glycine have already been implicated as inhibitory transmitters in the vestibular system, but apart from pertinent studies no quantitative histochemical determinations regarding the primary afferent transmitters have been carried out so far. Strong indirect evidence has indicated that aspartate may be a (or the) primary transmitter in the cochlear nuclei, and that glutamate may also be involved. It is not unreasonable to assume that one or both of these substances may also be the primary transmitter in the ontogenetically-closely-related vestibular system. The aim is to map the distribution of the four putative amino acid transmitters within the four main vestibular nuclei of the cat, as well as within several of the minor associated nuclei. A "block model" of these nuclei was developed in the cat, similar to that generated by others for the cochlear nuclei in order to provide a precise three-dimensional framework upon which to correlate these histochemical data from other disciplines. Following this aim it was planned to examine the effects of interrupting physiologically and anatomically well-defined afferent pathways upon the levels of the four putative amino acid transmitters in the vestibular nuclear complex. Reductions in the levels of the putative transmitters in the areas of nerve terminal degeneration would allow certain conclusions to be drawn about their role in neural transmission.

Laryngeal

Studies have been made of the symptomatology, etiology, course, and typology of spastic dysphonia. A temporary chemical paralysis of one recurrent laryngeal nerve (RLN), used diagnostically in some patients, was shown to be a good predictor of immediate post-surgical voice quality, at least for reduction of overpressure (strain) and post-surgical breathiness and aperiodicity. Vocal tremor and rate were found to be variably affected. Effects of chemical paralysis of the RLN on voice quality as related to the injection side (left vs. right RLN) have also been studied. The preliminary results indicate that perceptual differences pertaining to the injection side are not significant. Laryngoscopic signs of vocal-fold pathology are not seen except for quaver or tremor. Case histories vary, but a majority of patients report uneventful progressive onset. Although RLN section remains the preferred surgical technique, RLN crush was performed on four patients. In all cases, spasticity recurred when motion returned in the vocal fold on the crushed side. A reaction time (RT) study (initiation and termination of phonation at low-modal falsetto range) was conducted on five patients pre- and post-surgically. In all cases, faster reaction times were obtained post-surgically. Both voice onset and offset RTs were significantly slower pre-surgically, possibly indicating impairment of abductory and adductory control in these patients. More normal voice initiation and termination is achieved by a paralyzed larynx than by a "spastic" larynx. Seventy-two patients who underwent RLN section were evaluated from one to more than three years post-operatively by personal interviews, by perceptual judgments of pre- versus post-operative voice characteristics, and by acoustic measurements. Ninety percent report easier communication although, of these, 69 percent report problems in achieving desired loudness. Over 80 percent offered unqualified recommendations for this form of treatment. It was found that the voice tends to stabilize six to nine months post-operatively. If pre-operative voice symptoms (spasticity) recur, they will usually be apparent during the first year following surgery. In a few cases (all at least one year post-operatively), Teflon injection into the paralyzed fold was required to achieve better vocal volume. Perceptual ratings of pre- versus post-operative samples show marked decrease in overpressure, with some increase in perceived breathiness. Tremor, if initially present, may either remain or subside. Aperiodicity increases during the initial post-operative period, but tends to disappear thereafter.

The nature of the central nervous system control of the laryngeal muscles has been studied using electrophysiological and histological techniques. The studies comprised description of the underlying organization of primate laryngeal motor cortex, its role in various laryngeal movements, and its connections with subcortical nuclei. Satellite studies have also been performed to help elucidate the organization and relative roles of subcortical (brainstem) neurons in their various laryngeal functions (i.e., vocalization, respiration, and protective reflexes). The cortical representation of three intrinsic laryngeal muscles (cricothyroid (CT), thyroarytenoid (TA), and posterior cricarytenoid (PCA)) and one extrinsic laryngeal muscle (sternothyroid (ST)) has been ascertained. In each case, myotopic zones representing the CT muscle were located more rostrally along the posterior border of the arcuate sulcus in area FCBm, while those representing the TA muscle were located more caudally just anterior and inferior to the subcentral sulcus (dimple). The extrinsic laryngeal muscle was always found to have a separate and more caudal representation about the dimple, with no interdigitation of its zones with those of the intrinsic laryngeal muscles. Microstimulation at a given cortical site always resulted in activation of a single intrinsic laryngeal muscle. Although some interdigitation of zones of the TA and CT muscles were observed medially, where the representations of these muscles border one another, a single muscle was apparently represented in each zone. Interdigitation of zones may have a functional significance for these two muscles, since they act synergistically during vocalization in determining vocal cord length and tension. As yet, no cortical representation of the abductor muscle (PCA) has been found; its role in vocalization may be controlled subcortically. Myotopic zones were all of similar dimensions, approximately 500 microns in diameter. Pyramidal cells within a zone evidently projected to the same type of lower motoneurons, since the latency and size of EMG responses and contraction times of muscle units did not vary with stimulation within a given zone. A change in muscle response (as well as a change in threshold for activation) was used as a basis for identifying a single zone. The CT muscle appeared to have a relatively larger cortical representation, with a relatively greater number of cortical zones, than the TA muscle, which may reflect the prominent role this muscle has in vocalization.

Communicative Aids

The development of communication skills in children born profoundly deaf has been compared with hearing children using spoken English. A study was carried out in an educational setting which included integrated (main-streamed) classrooms as well as self-contained classrooms, and a study was carried out involving deaf children assigned to self-contained classrooms (deaf children only) and involving deaf and hearing children assigned to integrated classrooms (hearing children and main-streamed deaf children). The deaf children from the self-contained classrooms tended to use American Sign Language to communicate. The deaf children from the integrated classrooms tended to use speech and speechreading with some natural gestures. All of the deaf pupils wore Phonic Ear hearing aids matched in frequency to the microphone worn by the teacher. Data on individual S's hearing status have been coded and recorded on their performance records. Approximately one week before and one week after training, Ss were administered a referential communication test battery. The results replicated pervious findings in that a limited amount of supervised practice led to significant improvement. Oral deaf children and hearing children tended to experience more difficulty describing spacial relations than deaf children using American Sign Language (whose grammatical structure involved spacial organization as an important feature). In deaf-hearing dyads, spoken English prevailed as the dominant language. The results support an experiential deficiency hypothesis to account for deaf children's communication problems, inasmuch as a minimal amount of training led to substantial improvements. Previous research on young children's ability to deal with ambiguous messages has led to the conclusion that they are deficient in that they do not request additional information to clarify ambiguity. Further research, however, has confirmed that listeners develop the alternative strategy of inferring the speaker's intent on the basis of what he does not say as well as on the basis of the explicit contents of the message.

A research team has been assigned to produce external electrode devices and a single-channel wholly implantable receiver. These implantable hearing devices are essentially the same as first generation devices, except that the possible use of an FM (rather than simple RF) receiver is being investigated. (Advantages: small; less sensitive to external antenna placement. Disadvantages: more parts; greater probability of failure). The fabrication of these devices is straightforward. In the present schedule, receivers should be ready for bench testing in about 3 months. Based on surgical experience gained in the first 2 patients, and with incorporation of design changes indicated by psychophysical testing in these patients and by physiological studies directed toward defining "ideal" electrodes, these devices have been totally redesigned. The second generation devices should constitute devices of probably wide application. The strategy of implantation of a local wholly implanted receiver with a remote disconnect plug allows the patient full use of the device as an aid, while allowing use of the device to define "optimal" characteristics of higher order speech processing drivers and transmitter receivers. The design changes in the plug and its new location should virtually eliminate any possibility of infection. Finally, the simplification of the implantable disconnect plug will greatly simplify replacement surgery for either replacing defective receivers, or for replacing initially implanted receivers with higher-order devices.

The hypothesis that the sense of touch can convey a significant portion of information lost through profound deafness was studied in a target population including deaf children and adults. The study was designed to evaluate the effects of vibrotactile feedback, provided by a high-resolution tactile aid, on speech production in profoundly deaf children. A baseline measure of each child's speech was obtained by spectrographically analyzing the child's imitation of a speech stimulus. Consonant-vowel (CV) stimuli were presented by videotape, with auditory and lipreading cues available; the child was then encouraged to imitate the stimulus, and his response was recorded for spectrographic analysis. In half of the trials, the child received concurrent tactile information from the stimulus and from his own voice. The "teletactor" is an electrotactile sensory aid which displays acoustic information as touch patterns, via a belt worn around the abdomen. The belt contains 32 stimulators, spaced 1/2 inch apart, each of which responds to a specific sound frequency, thereby displaying frequency according to location on the skin. The 32 stimulators cover the frequency range from 80 to 8000 Hz, at approximately 1/4 octave intervals. The intensity of the sensation at each stimulator reflects the amount of energy present in each band, over a range of 30 dB. Six pre-lingually deaf children, ages 7 and 8 participated in this study. Three deaf/blind children participated in an identical procedure. All subjects showed an increase in the production of clearly defined second formant resonances for the vowels /i/ and /u/, while receiving tactile feedback. The subject exhibiting poorest speech also showed an increase in clearly defined first formant resonances for these vowels. The formant center frequencies for repeated syllables tended to be somewhat higher than those for sustained syllables, for all subjects. This finding may reflect the increased stress or effort required to produce repeated syllables. Abnormal high frequency energy was present in many utterances, in both conditions. For multisyllabic stimuli, more complete closures were produced in the tactile feedback condition. The difference described between the two conditions, (tactile feedback vs. no tactile feedback), are not statistically significant at this time. A completely wearable sensory aid, available on a day-long basis, would provide a significantly greater amount of useful information, and would produce a comparably greater effect upon speech production.

The Tadoma method has been the subject of a study. In this method, the observer receives speech by placing his hand on the talker's face. Current work concerned three areas: 1) determination of the character, extent, and effectiveness of Tadoma training and use; 2) the speech and language competence of deaf/blind, highly trained users of Tadoma; and 3) a study of the acquisition of Tadoma in normal-hearing, comparatively untrained subjects. A second mailing of a preliminary questionnaire (originally sent to 489 institutions listed in the 1975 American Annals of the Deaf Directory of Programs and Services) was sent to 775 facilities listed in the 1978 Directory. Of the 135 questionnaires returned in respones to the second mailing, 30-40% of the respondents had some knowledge of the Tadoma method; however, only 29 (or 23%) of the respondents had ever used the Tadoma method in teaching the deaf and/or deaf/blind. Information was obtained from these respondents regarding the types of children who benefitted most from Tadoma, the teaching outlines followed, the various hand positions used, and whether Tadoma was used alone or in conjunction with other teaching methods (e.g., sign language and speechreading). In addition, a list of "successful" Tadoma users and a list of past and present teachers of the method have been compiled from the survey. An analysis of consonant and vowel confusion data was performed using a sequential information analysis. The analysis, which assesses the contributions of predefined features to total transmitted information (TI), yields a set of features which contribute maximally and independently to TI. The features identified in the analyses for consonants were voicing, low, round, frication, and place. The effects of alterations in hand position on the perception of small sets of consonants and vowels was studied. Four major types of information (airflow at the lips, movements of the lips, movements of the cheek and jaw, and vibration on the neck) were assumed to be available to the Tadoma user. The data are currently being analyzed to determine the extent to which the physical cues supply independent or redundant information to the Tadoma user.

Language

A novel method for helping children learn to read has been evaluated. The method consists of presenting items (letters, syllables or words) successively, one at a time, on a TV screen in such a way that the item appears visually at that same time it is heard on the sound channel. The result is a word or sentence which "grows" left-to-right across the screen until the whole word or sentence is complete. The rationale for its use is that it shows how the letters and words in a sentence follow (succeed) each other, just as the sounds do when they are heard. In other words, the method provides the link between written and spoken language which must be learned by anyone who is ever to become a fluent reader. During the past year, experiments have been carried out in three primary-grade schools in the area. The experiments compare the effects of the dynamic visual display versus a static (control) display, and the measure is word recognition. The results and conclusions were 1) word-recognition scores favor the dynamic over the static display; 2) the training paradigm seems more useful than the within-subjects paradigm, since it tests transfer of training to the more normal static display (a more stringent test of results); 3) the pattern of results obtained so far with unselected subjects suggests a shift toward working individually and intensively with only the poorest readers; 4) experience gained from these studies suggests that the training paradigm may be appropriate for work with deaf children, but using subjects at older age levels in initial studies.

American Sign Language (ASL) has its own rules of syntax. Furthermore, in sentence contexts the basic sign units undergo meaningful modification of form by changes in movement and spacial displacements. The modifications prove to be a key to one of the salient structural characteristics of the language: its richness in morphological processes, which result in single sign units complex in form as well as in meaning. Research shows ASL has developed elaborate morphological devices in a form which is unique to a visual-gestural language. Morphological processes in English and other spoken languages--the means by which complex words are built from minimal meaningful units--typically involve the linear addition of phonological segments to words. ASL manifests no tendency whatever to build up its lexical units in this way. Rather, signs undergo a wide variety of grammatical processess--regular changes in form associated with regular changes in meaning--each of which operates by imposing different dynamic changes in movement and spatial contouring. For example, a process which embeds the sign stem in reduplicated smooth circular movement changes the meaning of a basis sign referring to a transitory state so that it refers to an inherant quality. Under this inflectional process, the sign QUIET means 'taciturn' or 'quiet by nature', the sign WRONG means 'error-prone' and so forth across a large class of predicates. Conforming with the unique spatial characteristics of this visual-gestural language, its morphological devices make structured use of space and movement, nesting the basic sign in spatial patterns or within complex contours of movement, thus creating single unit forms into which a great deal of information has been simultaneously compacted. For the form of its morphological processes, the mode in which the language developed appears to make a crucial difference. It is the dimensions of space and movement which the language uses for its grammatical processes: inflections in ASL involve superimposed spatial and temporal changes in the movement of signs. A single lexical sign can be built up in a multitude of ways in inflectional patterning to create complex single unit forms into which a great deal of information has been simultaneously compacted. The steps in the acquisition of this system by deaf children of deaf parents are being studied.

A battery of tests has been devised to assess the capacity of right-hemispheric patients to process complex linguistic materials such as stories, jokes and figures of speech. In addition, a battery of tests probing the nature of confabulation has been devised for presentation to any patient who exhibits frank confabulatory tendencies. The test battery has been administered to twelve patients with unilateral right hemisphere disease. In addition, it has been presented to a small sample of aging and younger control patients. The findings indicate that, while right hemispheric patients have no difficulty in standard phonological and syntactic processing, they exhibit difficulties in ferreting out the main points of the story from subsidiary points, in ascertaining the moral of the story, and in figuring out which portions of a story might be considered humorous, sad, or incongruous. Contrary to hypothesis, the patients do not exhibit particular difference in processing emotional or spacial information in the stories, though they may sometimes make inappropriate inferences from emotional information. In general, the subjects performed quite differently from aging patients: the latter group showed word-finding difficulties and lapses of memory but, in general, no difficulty in sifting out tangential from central information.

The role of sentence structure and the syllable in the phonological patterns of aphasic speech were assessed by reviewing spontaneous speech errors of aphasic patients in terms of the segmental attributes of phonological errors and the nature of the phonological contexts in which these errors occurred. Results suggest that the segment has its own integrity as a unit of speech processing and further that its structure is based on distinctive features.

However, the segment seems to be only a quasi-independent unit, as all types of phonological errors analyzed are sensitive to a larger phonological unit. Speech processing then involves the dynamic integration of all aspects of the grammar. Even at the level of articulatory planning and programming, segment structure interacts with syllable structure as well as with lexical and syntactic rules of grammar. Eighteen subjects (4 Broca's, 4 Conduction, 5 Wernicke's, one non-aphasic dysarthic, and 4 normal controls) were subsequently measured for voice onset time (VOT). Normals' productions are characterized by a cleancut separation of the two phonetic categories, as are the Wernicke's. In contrast, the Broca's manifest a phonetic production deficit as there is considerable overlap between the two phonetic categories. Further analysis revealed that they have a pervasive phonetic disorder which affects their correct target productions as well as the total number of phonetic errors produced. Comparison of the speech production of the Broca's patients and the non-aphasic dysarthic indicated that Broca's productions reflect a speech deficit rather than a low-level motor control problem. Thus, an acoustic analysis distinguishes the Broca's from the Wernicke's aphasics and suggests that the Broca's aphasics have a pervasive phonetic disorder superimposed on a deficit in the phonological organization of speech, whereas the Wernicke's aphasics show primarily a phonological deficit characterized by phonemic mistargetting. Twenty-four subjects - 4 non-brain-damaged controls, 4 right brain-damaged aphasics, and 16 aphasics including 8 anterior and 8 posterior patients were tested on the perception of a VOT continuum varying along the (d) - (t) phonetic dimension. Both labelling and discrimination functions were obtained from each subject. In addition, 12 of the 24 subjects were asked to read individual words varying in initial (d) - (t) and their productions were analyzed for VOT. Three patterns of perception were obtained: subjects could both label and discriminate the continuum; subject could neither label nor discriminate; and subjects could discriminate but not label the stimuli. The dissociation between discrimination and labelling ability was found for 3 of the 4 Wernicke patients tested and suggested that the basis for the deficit of these patients was not a sensory or low level of auditory processing, but rather at the level of phonological organization requiring the "use" of an auditory stimulus linguistically. A comparison of performance on the perception of VOT and auditory language comprehension revealed no systematic relation, thus suggesting that speech perception deficits (as measured here) cannot be the major factor contributing to language comprehension deficits. Finally, a comparison of VOT production and perception indicated a dissociation between these two abilities. In particular, anterior aphasics showed a phonetic production deficit and in general showed the ability to both label and discriminate VOT. In contrast, posterior aphasics showed a fairly normal production ability (save on occasional phonemic paraphasia) in the face of an impairment in labelling VOT stimuli.

The relative contributions of the right and left hemispheres to language processing in aphasia were examined by exploring the role which prosody plays in the sentence comprehension of the aphasic patient. Previous work has indicated that aphasic patients do not make normal use of grammatical morphemes--those elements of a sentence which function to indicate syntactic structure. This has been interpreted as a syntactic deficit. However, prosodically, these elements are unstressed, and therefore acoustically of short duration. It has been shown that processing difficulties in aphasia increase as stimulus duration decreases. One objective of this research is to address the question of the source of the syntactic difficulty: whether it is exclusively syntactic, or whether it is better seen in terms of prosody, and the acoustic correlates of prosody. In the latter case, it would be a special case of a general difficulty with temporal processing. A second objective is to test the hypothesis that prosodic intonation contours--holistic properties of sentences -- better provides information about sentence structure than grammatical morphemes for the aphasic. The rationale for such a conjecture is that intonation contours can be apprehended by the holistic processes of the right hemisphere, while the grammatical morphemes require internal analysis of a sentence by the analytic processes of the damaged left hemisphere. The set of studies thus explores how prosody on the one hand provides structural information in the form of overall intonation contours, and on the other hand, contributes to the syntactic deficit resulting from inattention to unstressed grammatical morphemes. The question of the relative contribution of the left and right hemispheres to language processing is of importance both to research in the area of aphasic language and brain function, and to the special health problems of the aphasic patient. Residual language functioning in aphasia either could be taken over by areas of left hemisphere adjacent to the lesioned areas, or be transferred to right hemisphere. The results of this study suggest that the right hemisphere is mediating language function, since the addition of intelligible sentences to intonation contours results in improvement of overall and left ear performance, but deterioration of right ear performance. If this greater contribution of the right hemisphere to aphasic language processing is born out by the rest of the studies of the project, this should have implications for the direction which remediation of aphasic language disorders might take.

The purpose of the research is to explore the characteristics of a right hemisphere mechanism for reading: specifically, (1) whether left hemisphere patients with the syndrome of "phonemic" or "deep" dyslexia are relying on a right hemisphere reading mechanism, and (2) whether right hemisphere reading capacities in normal subjects show the characteristic feature of reading performance in deep dyslexia (i.e., a reading vocabulary biased toward concrete nouns, and an inability to read functors). The principal experiments involve split-field studies of deep dyslexics and normal subjects: in the case of the dyslexics, to investigate the lateralization of reading mechanisms; and in normals, to determine whether there are different patterns of word recognition across lexical categories in the two visual fields. A major accomplishment has been the completion of a series of split-field studies on a small group of deep dyslexics. These subjects were run on a split-field lexical decision task at exposures set to control for possible perceptual deficiencies in the damaged left hemisphere (LH). Two of the patients showed a left visual field (LVF) superiority suggestive of a right hemisphere (RH) advantage for lexical decision. The third subject showed a small difference favoring the RVF. Overall, the visual field differences were not significant. Since visual input directed to one cerebral hemisphere by means of split-field presentation can readily be transferred to the other, the split-field task does not provide a very sensitive measure of the lateralization of reading functions. In an effort to increase the sensitivity of the task, the use of bilateral stimulation was used. When there is a competing stimulus in the LVF, the RVF stimulus should have more difficulty gaining access to the hypothesized reading mechanisms in the LH. The bilateral paradigm used in this study involved the presentation of a single letter to one visual field and, simultaneously, a lexical decision string to the other. The subjects had to respond to both stimuli. All three patients showed a LVF superiority for lexical decision under these conditions.

The objectives were to study the relationship between early language and sensory experience and the functional organization of the brain, using electrophysiological and behavioral techniques to assess and compare functional cerebral specialization in normal hearing and congenitally deaf adults and children. In these subjects (Ss), functional specialization of the left and right cerebral hemispheres for language (English and American Sign Language or ASL) and non-language tasks were described. Additionally, the possibility that the cortical areas which subserve audition and speech in normal hearing Ss have become functionally reorganized to process visual information in Ss deaf since birth, was investigated. The responses evoked over different brain regions while eleven congenitally deaf and thirteen normally hearing adults read English words were studied. Words were presented either to the left or right visual field or bilaterally (two different words to the two fields simultaneously). One second after each presentation Ss wrote the word(s) they had seen. Event-related cerebral potentials (ERPs) were recorded from the left and right hemispheres over occipital parietal, temporal, anterior temporal and frontal cortex, from the vertex and from under the left eye. Every hearing S accurately reported significantly more words after presentation to the right than to the left visual field. In contrast, the deaf Ss did not show any behavioral asymmetries in these tasks. ERPs to the words were characterized by posteriorly distributed negative wave, latency 200 msec (N200), and an anterior positivity, P250. In hearing Ss ERPs contained an additional, prominent negative event at round 400 msec (N400) followed by a slow positive shift (P700); this N400-P700 event was consistently (in every hearing S) larger from the left than the right parietal and temporal electrode sites. In marked contrast, ERPs from the left hemisphere of deaf Ss simply returned to baseline after P250, and did not display the N400-P700 event. On the other hand, right hemisphere ERPs from deaf and hearing Ss were identical. These data suggest that N400 and P700 reflect the activity of a specialized neural system in the left temporal-parietal cortex which is active during reading in normally-hearing Ss. The absence of this electrical event in deaf Ss may be related to the lack of the processing advantage of words presented to the left hemisphere in these Ss. Further studies are necessary to determine whether this reading-related ERP develops in the left hemisphere with the acquisition of any first language (English is usually the second language for deaf Ss) or whether it develops when language is acquired through the auditory modality (as English was in our hearing Ss, but not for our deaf Ss). These studies and others are designed to clarify the relationship between early sensory and language experience and the functional organization of the brain. Evidence gathered to date suggests that the two hemispheres are not functionally preprogrammed, but develop in response to the particular characteristics of the language first acquired. Similarly, we have discovered evidence which suggests plasticity may exist in sensory-neural structures in the human brain whose functions may also be partially determined by early environmental stimulation. The further study of neural plasticity in man will contribute important information concerning those environments which optimize sensory and language development in children.

Speech

Research on the effect of speaking clearly on the intelligibility of speech for impaired listeners has been initiated in order to obtain background information for new methods of matching speech to residual auditory function. In addition, the information gained from this work may contribute to the training of individuals who communicate orally with the hearing impaired, to the development of procedures for accounting for speaker differences in intelligibility testing, and to basic speech science. Preliminary measurements of the intelligibility of clearly- and conversationally-spoken sentences have been made for four listeners with sensorineural hearing loss. Substantial differences in intelligibility scores (18 percentage points) associated with speaking mode were obtained by each listener. Measurements made on the speech waveforms indicated that in clear speech the durations of all speech elements and the number of pauses per sentence increased, and vowels more closely approached target values, but consonant-vowel amplitude ratios increased only for selected consonants. Additional studies currently in progress are concerned with establishing the generality of these results and relating the improvements in intelligibility to changes in the acoustic properties of speech elements associated with the attempt to speak clearly.

Another investigation involved a longitudinal study of /s/ misarticulating-children. Because, in time, some kindergarteners will self-correct and others will not, a detailed study of misarticulating children from kindergarten through second grade should reveal the developmental patterns of each group. Children displaying defective /s/ production were chosen because /s/ is a frequently misarticulated sound. The major study involved the classification and analysis of the initial 55 /s/-misarticulating kindergarteners. Results, briefly, are as follows: there were 19 females and 36 males, with 35 interdentalizers, 6 lateralizers, and 14 retractors (others); 24% self-corrected, 13% improved, and 63% maintained. Profiles of improvement showed slow-steady, rapid-rise, and jagged patterns across time, in the first full year. There were no strong group effects of phonetic context. A companion study of cluster and individual patterns in the group of self-correctors in nearing completion. Another completed study detailed through acoustic descriptions the archetypal patterns of children's normal, interdentalized, retracted, and lateralized /s/ productions. An extension of these spectrographic patterns via analysis-by-synthesis procedures verified the consistency of correct/incorrect /s/ production patterns and specified more completely the descriptive parameters associated with each. Possible difference between normal and defective /s/ children in perception and jaw carriage are currently being investigated.

Another study was planned to determine the acoustic characteristics of the speech of the deaf. A major finding has been that there is a common pattern of error substitutions and omissions and that the error patterns of individual deaf children can be predicted, with a few exceptions, from this error matrix and an estimate of the child's overall error rate. The study model has been refined so as to identify articulatory error types and their relative frequency of occurrence that would produce this common error matrix.

Acoustic data from ordinary speech were used to produce a display of the movements of the vocal organs that might have produced that speech. Thus, instead of merely "lip reading", the deaf would have available a display that would allow them to "tongue read" as well, perhaps eventually enabling them to communicate over the telephone. During the past year the viability of a scheme that permits the generation of vocal tract shapes that could have produced simple sentences which contain only a few consonants was demonstrated. Three speakers saying utterances that contained mainly vowels and vowel-like sounds, like "We owe you a yoyo" and "Where were you a year ago?" were recorded. The first three formant frequencies were determined using a computerized LPC system. In addition we also used spectrograms of these utterances to correct and hand edit the LPC files. It was not the purpose to develop a formant tracking system as a major part of our work. Possible positions of the body of the tongue in these utterances were determined from the two parameters, front raising and back raising, which have been shown to specify the shape of the whole tongue. The algorithms for relating formant frequencies to these two parameters were determined by multiple regressions. A third tongue shape parameter has been added to the previous system to include the bunching that many speakers use in the r-colored vowels of American English. The algorithms were quite successful in producing plausible pictures. The system incorporates some kinds of allophonic effects, as for example the different degrees of tongue raising in the initial and medial semivowels in yoyo, due to the different degrees of stress. It is also possible to see some coarticulatory effects, such as the anticipation of lip rounding during the first sound in you. There was no difficulty in reconstructing plausible vocal tract shapes for each of the three speakers. These may of course not have been the shapes that were actually used, but shapes like those generated could have been used to produce most parts of these utterances.

The utilization of peripheral receptor information in the motor control of the lip movements for speech has been studied by stimulating the perioral and auditory receptor systems during lip muscle contractions for various speech and nonspeech gestures. Observations on the voluntary and reflexive electromyographic (EMG) responses of the perioral major system were then used to infer the characteristics of the underlying neural control processes and their function in speech production. Preliminary findings indicate that short- and long-latency excitatory effects are produced in various perioral motor units by mechanical stimulation of the lips. Some of these effects appear to be muscle specific (e.g., only inhibitory effects on platysma motor units) suggesting that the central projections of perioral mechanoreceptors to motor units may possess a functional organization having significance for orofacial motor control processes such as speech. There is some indication that measures of the peristimulus discharge pattern of the individual motor units may provide a more direct and sensitive indication of the effects of afferent stimulation when compared with the amplitude measures of the complex summed activity of several motor units.

Recordings from the levator palatini, superior and middle pharyngeal constrictors, palatopharyngeus and palatoglossus muscles of three speakers confirm that the levator palatini is the primary muscle of velopharyngeal closure. The other muscles do not work synergistically with the levator palatini. The implication of earlier work is that the mechanism of velopharyngeal closure is more like that of a trap door, than that of a sphincter. That is, the basic gesture in velopharyngeal closure is the elevation, and retraction of the velum and concurrent movements of the lateral pharyngeal walls result from the position of the levator palatini in the lateral walls, and not from synergistic contraction of the superior constrictor. In a test of the hypothesis, a high correlation was found between patterns of velar elevation and lateral pharyngeal wall displacement. In addition, the effects of phonetic content were similar for both lateral wall and velar displacement. In an extension of work on the effects of phonetic content on variations in velar elevation, velar elevation during both oral and nasal consonants was strongly influenced by the quality of surrounding vowels, being higher in high- than low-vowel environments. The results of studies of velar elevation and of EMG activity in the velopharyngeal region have provided the base for a model of velopharyngeal function requiring the specification of both temporal and spatial parameter values.

The muscles responsible for raising and lowering the mandible during speech have been examined in a study combining EMG and jaw-displacement recordings. The speakers' occlusion types were determined, to provide insights into the basis of individual differences in muscle function. The results of the study support the traditional descriptions of several muscles as jaw elevators or depressors for non-speech maneuvers, but not for speech gestures; for speech gestures the medial pterygoid and the superior lateral pterygoid and elevators of the jaw, and the anterior belly of the digastric and inferior lateral pterygoid are depressors of the jaw. EMG techniques have been used to clarify a classic phonetic problem. Traditional articulatory descriptions of front rounded and unrounded vowel pairs have described tongue height as being the same for the members of the pairs (i-y), (e-ø), and (-oe). Recordings from the genioglossus, mylohoid and anterior belly of the digastric muscles show differences in pattern for pair members in Dutch, implying that tongue position must be different and in addition clarifying the role of the three muscles in positioning the tongue. In another ongoing study of the tongue muscle function in vowel production, two patterns of genioglossus muscle activity, one for each of two groups of speakers have been shown producing the same set of vowel "tension" distinctions. These differences in tongue muscle activity are reflected in differences in the formant frequency relationships among the vowels of each speaker. In a cinefluorographic study of lingual articulation in consonant clusters, two alternative articulations for /s/, are seen in different speakers. The fact that many speakers judged as having normal articulation produce /s/ with the tongue tip behind the lower incisors has important implications for therapeutic strategies for individuals identified as having defective /s/ articulation.

In other studies, palatometric measures of the /s/ medial groove were obtained from utterances of 3 normal male adults. Electrodes on the pseudopalate were spaced at 2 mm. Twenty to 25 repetitions of the test sentence "Say __________ again" were obtained from each subject. In the consonant cluster study test words consisted of spat, smack, slack, snack, stat, stack, and scat with sat and sack included as control words. In the /s, z/ study six /h CVC/ nonsence words were used. Results showed that the /s/ medial groove width was 6 to 8 mm. It was about 2 mm wider for stat, sat and stack. For all test words studied, the minimum /s/ groove was most frequently found within 30 msec after the onset of frication. Cessation of the minimum groove was most abrupt for the clusters with the alveolar sounds /t, n, l/, more gradual for the clusters with the bilabial sounds /p, m/, and most gradual for the /sk/ cluster and the prevocalic /s/'s. In all instances the release of the /s/ groove was more gradual than its formation. These results indicate that release of the minimum anticipates the articulatory requirements of the sound which follow. In general the prevocalic /s/'s showed a substantially reduced area of contact at the termination of acoustic frication. However, for the /sp, sm, sk/ clusters, the area contacted remained virtually unchanged for 50, 40, and 20 msec respectively beyond the frication offset. Spectrographic data for the /sp, sm/ clusters often evidenced an abrupt transition at the end of the /s/ frication. These results suggest interstructural apical-labial reciprocity and intrastructural apical-dorsal reciprocity during the /s/C clusters.

A study has been carried out concerning the relation between syntax and phonetics in the processing of human speech. A principal goal is the development of a theory of syntactic-to-phonetic coding in speech production, a theory that should provide a basis for work on such practical problems as speech synthesis and treatment of deaf children's speech. The major theoretical development is embodied in the theory of syntactic-to-phonetic coding. This theory is designed to describe syntactic influences on four speech attributes: pauses, segmental lengthening, cross-word phonetic conditioning, and fall-rise patterns of fundamental frequency, all of which may accompany syntactic boundaries. The theory includes a metric for calculating the strength of a given syntactic boundary and then determines the influence of extra syntactic factors, including speaking rate, constituent length, and others. In addition to this general theory, a number of inferences about the speaker's structural representation and processing of syntactic information have emerged from a consideration of the empirical studies. The major recent empirical development is the completion of a large-scale study on fundamental frequency. This study included experiments on the properties of declination, fall-rise patterns, and blocking of cross-word conditioning effects of fundamental frequency. The empirical studies on declination revealed effects of planning on the part of the speaker, and a consideration of these effects led to new hypotheses about the role of speech planning in sentence production.

A method has been developed for estimating the vocal tract shape from acoustic speech signals. The relationship between vocal tract configurations and their corresponding frequency characteristics is of utmost importance since the vocal tract shapes must be estimated from acoustic parameters. A computer simulation of the transmission line analog model of the vocal tract has been completed. For the purpose of strict evaluation of the model performance, the frequency domain simulation is used. Using this model, the contributions of different parts of the vocal tract to increments in a given formant frequency were investigated. The sensitivities of the formant frequencies to given parts of the vocal tracts were also computed for the simulated diphthongal utterances. The behavior of the higher resonance frequencies is currently being investigated. This will lead to rules to extrapolate the frequency characteristics of the vocal tract beyond those available from the acoustic speech signal so that the smooth vocal tract shapes can be obtained rather than 8-section discrete shapes.

It has been hypothesized that invariant acoustic cues for place of articulation can be derived from the short-time spectrum at consonantal release. These invariant properties can be characterized in terms of the gross shape of the spectrum and theoretically provide the listener with perceptual invariance independent of context-dependent effects. Current research attempts to assess this model by investigating whether invariant arcs for place of articulation are perceived independent of context effects signalled by vowels. Further, to delineate the nature of the perceptual mechanism for interpreting the window or frame of analysis for onset spectra in relation to spectral discontinuities has been attempted. The study attempted to determine whether acoustic invariance might be derived from a simple property sensitive to the frequency in which the highest energy peak of the spectrum falls, rather than from a more complex property sensitive to the overall shape of the spectrum. Comparison of the spectra for initial stop consonants in terms of their shape or location of prominent energy peak revealed that unlike the templates characterizing shape, the frequency analysis categorized only 53% of the utterances; vowel context effects were found for particular consonants; and overlap between the alveolar and velar categories was found in the frequency range 3000 - 3500 Hz. The perception of onsets of natural speech was explored to determine 1) if onsets provide sufficient cues for place of articulation, as was found for synthetic speech, 2) if the perception of these onsets was vowel dependent, and 3) if vowel context effects for perception of these onsets were similar to those found using the template-matching procedures. Results showed that onsets provide a reliable cue for place of articulation in natural speech, although the level of performance is lower than with synthetic speech. Further, vowel context effects were shown in perception and these were similar to those found in the templates-matching procedures. These results suggest that onsets provide sufficient cues for the perception of place of articulation and that the templates capture critical characteristics of the perceptual processing mechanism of speech.

Speech is a highly encoded acoustic signal related in a complex way to the perceived phonetic segments of the language; that is, the consonants and vowels we hear when we listen to speech. A critical issue in the investigation of speech perception is the description of the mechanisms by which the information in the speech signal is analyzed in order to arrive at the identity of these perceived phones. It has recently been proposed that phonetic information is extracted from the speech signal by channels of analysis, similar to those that exist for the analysis of visual information. There is now considerable evidence that such mechanisms exist and that they are operative either at or shortly after birth, strongly suggesting that these mechanisms are part of the human's biologically endowed capacity to acquire and use language. The tuning and operating characteristics of the analysis systems have now been examined. The tuning functions of the analysis channels were examined first; then the degree to which particular channels are sensitive to context; and third, the operation of these channels as affected by changes in suprasegmental variables such as speaking rate. Evidence for a very broadly tuned channel, sensitive to voice-onset-time information underlying the voicing distinction between /b/ and /p/, has been found. That finding on an additional subject has been replicated and two additional channels, specifically, the channel analyzing transition duration information specifying a /b -wa/ distinction. For both of these channels, unlike the voicing channel, there appears to be a relatively narrow tuning, such that the effective information for the channel spans a relatively limited range. A series of experiments used a selective adaptation technique to examine the dependencies that arise in processing phonetically-relevant acoustic information in syllable-initial consonants. The pattern of results, identical across two vowel contexts, indicates that voice-onset-time specifying a voicing contrast (/b/ vs /p/) and the spectral form of the initial transitions specifying a place of articulation contrast (/b/ vs /d/) are processed in a mutually dependent fashion. A different pattern was revealed, however, for the processing of the spectral form of the transitions specifying a place contrast (/b/ vs /d/) and the duration of the transitions specifying a manner contrast (/b/ vs /w/). The data indicated that transition duration is processed independently of the spectral characteristics of the transitions, even though the processing of the spectral characteristics of the transitions is dependent on their duration. This pattern of results indicates first, that there are distinct patterns of interaction during speech processing; second, that the system does not operate entirely in a context-conditioned fashion; and third, that at early stages of processing the speech signal is not treated holistically, but rather undergoes analysis in terms of those acoustic dimensions that provide information about phonetic distinctions.

Several experiments in the acoustic, articulatory, and perceptual characteristics of particular segmental phonetic features have been carried out. Through simultaneous measurements of contact between tongue and lower teeth and of the acoustic characteristics during the production of these consonants the nature of the quantal differences between these sounds has been determined. The distinctions among the various consonal stop consonants have also been examined through acoustic analysis, and this study has led to the conclusion that tongue body position (as opposed to tongue tip position) plays an important role in these distinctions. The work with the coronal consonants is aimed at gaining a better understanding of the acoustic and articulatory correlates of the distinctive features that classify these consonants and, if necessary, revising these features. Preliminary acoustic data have also been obtained on the distinction between consonantal and nonconsonantal segments (rapid versus slower rate of change of some measure of overall amplitude), between voice and voiceless segments (presence versus absence of low-frequency periodicity in the vicinity of a consonantal boundary), and between nasal and nonnasal segments (presence versus absence of substantial low-frequency energy during the interval of consonantal closure). In a series of experiments on spectrogram reading, experience with the study of phonetic recoding phenomena demonstrated that phonetic transcriptions of sentences can be achieved from visual examination of spectrograms with good accuracy by an experienced observer. The results suggest that an acoustic signal carries much more information concerning the phonetic content than was previously thought.

Touch

One study concerned the perception of weights applied to the skin and how their apparent heaviness depends on temperature, body region, body side and sex. In all body regions cold objects were judged to feel heavier than neutral objects, usually much heavier. Cold intensification appears to be a general feature of cutaneous sensation. In contrast, warmth intensifies heaviness clearly in some regions but not in others. Some body regions (e.g., the palm) are more sensitive to weight than others (e.g., the back), and this superiority correlates with capacity for 2-point discrimination and point localization. Also, the right side shows a small but significant overall greater sensitivity than the left side. There were no detectable sex differences. The complexity of sensory input from the skin in ordinary experience contrasts with the simplicity of sensory stimulation in the laboratory. The study of the senses in isolation under careful control has been useful and indeed necessary in order to provide an accurate description of the functional properties of the skin. Yet a variety of experiments show the existence of interactions among these sensory domains that show that the richness of sensory experience from the skin reflects far more than simple addition of sensations from separate dermal modalities. An accurate functional description of the dermal senses offers a much needed link between the controlled world of the laboratory and the complexity of normal sensory experience; but such a phenomenon might have some practical communication advantages for individuals with sensory deficits (e.g., the blind and the deaf). Interactions between temperature and touch might provide means by which additional channels of information could be made available to individuals using devices that transform visual or auditory information perceived via the dermal senses. Taste, touch, and temperature have obvious importance for food and fluid intake. The interactions among these sources of stimulation are already known to change the perceived intensities of some of the stimuli. For example, moderate concentrations of sucrose warmed to body temperature are sweeter than sucrose at room temperature and the saltiness of NaCl may prove to show very similar changes with temperature. These modifications of the perceived intensity of sweetness and saltiness have special interest because of the health implications of consumption of sucrose and NaCl. The perception of temperature in the mouth has been related to satiation of thirst. Therefore any interactions between taste and perceived temperature could have implications for fluid intake.

The capacity of the skin for processing complex spatio-temporal patterns has been examined by varying the dimensions of locus, duration, intensity, and frequency of vibration of a multicontactor computer-controlled display. The effect of changing the site of stimulation of the multicontactor array from the thigh to the palm of the hand, and the problem of "loudness", number, and intensity of vibrators in the array have also been examined. A new vibrotactile matrix was constructed in such a way that it could be driven by the computer exactly as the thigh matrix is, but on a scale such that all 64 vibrators fit on the palm of the hand. With this device, 10 subjects were tested for pattern discrimination in a paradigm that varied pattern communality from 0 to 90 percent. Results compare favorably to those obtained on the thigh, i.e., the curves relating communality to errors are very nearly identical.

The fine structure and histochemical characteristics of the peripheral sensory and autonomic end organs have been correlated with their functions under normal, experimental, and pathological conditions. Neurohistological, electron microscopical, and histochemical studies were carried out on human hairless digital skin and on hairy body skin that was involved in various kinds of urticaria. Using serial sections and graphic reconstructions of osmium-fixed digital skin, the fine morphology and microtopography of the free nerve endings were studied electron microscopically in a total area of five square millimeters. It was found that the digital skin accommodated up to eight dermal papillae and three to four sweat duct orifices per square millimeter. Each papilla contained one to three fenestrated capillary loops. More than 60% of all papillae contained free nerve endings, sometimes up to five in a single papilla. As a result, up to one hundred free nerve endings were counted per square millimeter containing approximately 250 axon terminals. Intraepidermal endings were also present, one to five per square millimeter. No endings of any kind were found within the boundary zones between the papillary ridges and in the immediate vicinity of the sweat ducts. The origin of a free ending was marked by the perikaryon of a modified Schwann cell which constituted the terminal cell of the Schwann sheath. The perikaryon was situated at the base of the dermal papilla, while its distal process provided the cytoplasmic sheath to the axon terminals and their branches.

In a study of psychophysical and neural responses to thermal stimuli, the goal was to chronically implant chambers in the skulls of monkeys that would allow recording from active cortical units in the awake animal. The second goal, under this general aim, was to develop an automated search-measurement program for the application of thermal stimuli to the palmar surface of the hand during the time the cortex was searched for units activated by thermal stimuli. In the second objective--measurement of the return of sensation to grafted skin--the principle aim was to develop a means of characterizing the return of tactile sensitivity to grafted skin. It is known that normal skin varies considerably from point to point in its sensitivity to mechanical deformation. The first question to be addressed had to do with the specific aspect of deformation, i.e., depth of indentation versus velocity of indentation, that characterized the appropriate metric for tactile sensitivity. The second goal was to determine if an adequate measure of tactile sensitivity would be to count the peaks and measure their heights in terms of velocity or depth of indentation. A search of the cortex for thermal units was completed with a series of observations using various dental acrylics and means of implanting chambers and head-restraint bolts. The study indicates that moderate-to-good retention of the implants can be achieved with the current chamber design and the use of "Duz-all" dental acrylic. An automated program consisting of two parts, the search program and the measurement program, was developed. The search program consists of 20°C temperature swings, between 20° and 40°C, at a frequency at 0.05 Hz applied to the palmer surface of the forepaw. The measurement program consists of presenting steady state temperatures at 5° intervals between 20° and 40°C and measuring the activity in selected cells at each temperature step. After measurement of steady-state activity, measurements of the dynamic response to 1, 2, and 5°C temperature changes at the rate of 2°/sec will be made. In the study of the return of sensitivity to grafted skin, the biggest problem was characterization of the skin's response to mild mechanical stimuli. To this end, several studies involving measurement of sensation at threshold and suprathreshold intensities of stimulation as functions of the velocity and depth of indentation were completed. At threshold levels, velocity had a profound effect until it reached the rate of indentation of about 0.1 mm/sec. At higher rates of indentation, no further decrease in threshold was found. At suprathreshold levels, velocity had a distinct effect upon the magnitude estimates of the sensation for all velocities up to and including 10 mm/sec. However, depth of indentation seemed to have a far greater effect on sensation magnitude than did velocity. The research involving thermally sensitive cortical units will provide basic information about the functioning of the temperature sense and represents the only study in which comparisons of cortical activity, peripheral nerve activity, and behavioral measurements of temperature sensitivity can be made by use of the standard set of conditions of stimulation. The basic information provided here may aid in a better understanding of why some cases of penetrating head wounds show loss of temperature sensitivity, while experimental studies employing ablations have, so far, failed to demonstrate such loss. The significance of the return of sensation to skin graft should provide the clinician with a basis for the selection of the type of grafting procedure for maximum sensory return and an expectation of the time and degree of sensory return to the graft. The test battery, in its final form, should not only aid the plastic surgeon in estimating the degree of recovery following grafting but should also be of interest to the neurosurgeon in establishing the degree of recovery that has occurred following peripheral nerve repair. The results in such a sensory testing program should also be of considerable importance to the neurologist in diagnostic procedures.

Taste

The brain stem taste centers show an extraordinary competence in independently guiding gustatory-related behavior, including activity formerly thought to be associated with telencephalic mechanisms. Decerebrate rats, deprived of all neural tissue above the collicular level, show precisely the same orofacial mimetic responses to taste stimuli as do normals, including acquisitive reflexes for appetitive tastes and expulsive, flushing reflexes for those which are aversive. Thus taste discrimination in the rat is complete, and motor responses integrated at, or caudal to, the midbrain. Similarly in humans, anencephalic neonates, whose sensory-motor integration was restricted to the brain stem, showed facial reactions and acceptance-rejection responses which were identical to those of normal neonates. Moreover, when the forebrain is intact, it does not appear to be an aid to taste discrimination: solitary tract neurons are more accurate predictors of discrimination behavior than are taste cells in the rat thalamus. Thus acceptance and rejection in the gustatory environment are adequately managed by the brain stem, both for lower animals and humans. These are most likely inherited abilities, as can be shown by the elicitation of sucking from a human fetus by the injection of saccharin into the amniotic sac. Approach to and avoidance of chemicals could be seen as purely reflexive, a sophisticated extension of bacterial chemotaxis, while the powerful hedonic attributes of taste could be organized in the forebrain. That this is not the case is implied by the responses of the anencephalic neonates who responded not only with acceptance or rejection, but also with well-integrated responses appropriate to the taste: smiling and indications of satisfaction for sucrose, and crying and anger to quinine.

The objectives of a study of the physicochemical aspects of taste were to gain insight into the surface chemical processes attending and modifying the interactions of tastants with taste receptor membranes. The effects of variable surface charge, ion-binding and diffusion on the microenvironment of phospholipid monolayers have served as models for the receptor surface. This model seems appropriate in view of reports that charged phospholipid may play a role in salt and acid reception. The results suggest that the "water" response in man and other mammals may involve a local increase in acidicity as salt is removed from the system. The studies have led to a model of acid and water responses based upon the surface properties of charged phospholipids. The model suggests that the receptors may be responding to changes in surface pressure induced locally by changes in salt concentration. It further suggests that any ion effect is a composite of 1) specific ion-receptor association, and 2) nonstoichiometric electrostatic effects common to all ions. If surface pressure changes in the receptor membrane play a role in transduction, agents which specifically change the surface pressure might be expected to interfere with normal transduction. Since direct increases in H^+ ion concentration and Ca^{++} ion concentration result in decrease in the surface pressure, it seems reasonable to postulate that surface pressure decreases are excitatory in taste reception whereas increases are inhibitory (or at least neutral).

The goal of another study was to compare and contrast the central organization of the facial and vagal gustatory systems. Anatomical tracer studies demonstrate that the facial and vagal gustatory channels maintain relatively separate lemniscal systems through thalamic levels. Studies entailing localization of L-enkephalin indicate a third, hitherto undescribed system that accompanies the ascending gustatory paths at least as far as the isthmic level (superior secondary gustatory nucleus). Although both the vagal and facial lobes contain enkephalinergic fibers, a dorsolateral cap of the vagal lobe is especially heavily laden with enkephalin-containing processes. This pattern is mirrored in the superior secondary gustatory nucleus in which only the extreme lateral portion contains high levels of enkaphalin. Preliminary studies with HRP confirm that the enkephalin-rich cap region of the vagal lobe projects to the lateral, enkephalin-rich region of the secondary nucleus. The other portions of the secondary nucleus receive their input from the facial or vagal lobes proper. By relying on anterograde transport of HRP from the gustatory lobes in catfish, the vagal and facial gustatory channels are identified as not entirely independent within the superior secondary gustatory nucleus. However, despite the cross-talk between channels, a given portion of the secondary nucleus receives the bulk of its input from only one of the gustatory lobes.

The objective of another taste study has been the central basis for taste-quality coding. Of particular interest is a careful investigation of the response properties of taste-responsive neurons at different levels of the hamster central nervous system and a comparison of these data to behavioral judgments of taste quality by these animals. The objective is to eventually record from taste-responsive cells at all levels of the hamster CNS to which gustatory information projects, including the classical brainstem-thalamus-cortex pathway as well as the projections into the ventral forebrain, using both acute and chronic recording techniques. It was found at both levels of the hamster brainstem that the across-neuron correlation profiles, suggesting that the across-neuron pattern of activity is a viable candidate code for taste quality at these levels of the nervous system. However, because of the increased breadth of tuning of the sucrose-best cells in the pons, which are much too broadly responsive to correlate with the behavioral specifity among these stimuli, the notion of a labelled-line coding scheme is not particularly salient at the pontine level.

In a study of the central origins of cranial nerve parasympathetic neurons, using retrograde transport of horseradish peroxidase (HRP) the central origins of efferent axons in most branches of the facial, glossopharyngeal, and vagus nerves were examined. Using ten separate nerve preparations, organization of the superior and inferior salivatory nuclei as well as the lacrimal nucleus and the efferent neurons innervating glands of the posterior tongue was reconstructed. The picture revealed by this data was sufficiently different from the descriptions found in textbooks that it will require confirmation in primates. Central distribution of cranial nerves V, VII, IX, and X is a replication of earlier work. Nanoliter quantities of labelled proline or leucine were injected into the ganglia associated with these four cranial nerves; their transport into the medulla inside the axons was plotted by coating frozen sections with photographic emulsion. The projection of VII, IX, and X into the spinal trigeminal system appears to be denser than previously recognized. The extent of overlap in primary afferent terminations of V, VII, IX, and X within the nucleus of the solitary tract can be more precisely mapped, and may lead to better understanding of the functional interactions among the various sensory modalities represented in these nerves. A previously unrecognized contingent of vagal axons terminates in area postrema, a circumventricular organ long thought to function in the monitoring of blood-borne toxins. The anatomical organization of the subdiaphragmatic vagus began in an attempt to delineate the central terminations of afferent axons innervating the stomach, small intestine, and transverse colon.

Smell

In the histopathological investigation of dysosmia, biopsies of olfactory mucosa from dysosmic persons, with minimum risk and tissue damage to the patient, are essential. Original biopsies with standard equipment yielded only respiratory epithelium. It is very difficult to obtain proper specimens, since a) the area populated by receptors is small; b) the area is difficult to reach; c) the investigator using standard equipment cannot see the "target area"; and d) the cribriform plate is all that separates the biopsy instrument from the brain. These difficulties may explain why several published studies which purportedly describe the fine structure of human olfactory epithelium actually describe tissue samples of respiratory epithelium. Olfactory dysfunction is a significant problem in public health; one and one-half million U.S. citizens are annually afflicted by olfactopathy. In spite of its common occurrence little is known about olfactory pathology. In fact, little is known (compared to our present level of knowledge of the visual system) about the structure and function of the normal human olfactory system. The dearth of information available about the structure and function of the human olfactory epithelium represents a substantial gap in our knowledge that we propose to fill. Ongoing investigations into the ultrastructure of the olfactory mucosa and the histopathology of olfactory dysfunction will generate significant contributions to the biomedical literature and will lay the ground work for the solution of a basic problem in public health.

A project has been established to determine the processes involved in transport of odorous substances within the olfactory epithelium and to discover the processes involved in the initial interactions between stimulus and receptor cell. Differential interference contrast observations on excised living tissues from the nose of the frog reveal that there are several morphologically distinct cilia types and that these are not homogeneously distributed. Cilia on the cells of the respiratory epithelium are short and move rapidly and metachronally. Under normal conditions cilia on the neurons of the olfactory receptor epithelium fall into three distinct classes, distinguishable on the basis of length and movement--streamers, strokers and wigglers. Streamers are long and immotile. They remain immotile in spite of changes in the physcial or chemical environment. Strokers are of an intermediate length and move in a low, whiplike fashion. Movements of neighboring strokers are uncorrdinated and asynchronous. Wigglers are short and move quite rapidly. Sometimes the motions of the cilia in an epithelial patch are coordinated in metachronal waves. Wiggler motion velocity is much less rapid and is different in form from that of cilia of the cells of the respiratory epithelium. The cilia types of the olfactory receptor epithelium occur in patches 50 to several hundred microns in diameter. Boundaries between patches are startlingly abrupt. The entire epithelium is ciliated, i.e., there are no patches lacking cilia of one type or another. Some patches are mixed with cells sporting one cilia type interspersed with cells of another type. In patches with cilia of two types, the types are sharply distinguishable. This is not to say that a wiggler cannot become a stroker or a stroker become a streamer as a growth process, only that the metamorphosis is an abrupt event. Structurally wigglers appear to be conventional cilia with the 9 + 2 axoneme structure and dynein bridges. Streamers and strokers have a wiggler-type proximal section and a distal section with reduced filamentary structure and no bridges. Different cilia types are also distinguishable on the basis of the properties of their outer membranes. The host cell at a certain stage of its development changes the properties of the ciliary membranes synthesized and elaborated at the cilia base; differing membrane properties appear to control the differing motion parameters by regulating access of calcium to the contractile structures in the proximal part of the cilium. In response to osmotic stress an aberrant cilia type can be seen. It is short, immotile, and has a diameter 5 or more times that of other cilia. We call these bristles. Finally, there is a fifth type which is a juvenile stage. During the first few hours following deciliation of the epithelium with 0.5% detergent solutions patches of short cilia which are not responsive to external stimulation develop. A few hours later these patches mature to become like those seen in mature epithelia except that the several cilia types are of shorter lengths. All observations lead to the conclusion that the cilia grow rapidly and continuously and differentiate into functionally different species.

The objectives of another project were: 1) to anatomically define the central nervous system pathways arising from the olfactory and vomeronasal organ receptors, which mediate copulatory behavior in the Syrian hamster; 2) to identify the non-chemosensory brain pathways which converge with olfactory and vomeronasal inputs to the amygdala, entorhinal cortex, frontal cortex and bed nucleus of the stria terminalis; and 3) to observe the effects of lesions in selected areas along these chemosensory pathways on the males's mating behavior. The efferent projection areas of the "vomeronasal amygdala" (the medial nucleus, M, and the posteromedial cortical nucleus, C3 and those of the "olfactory amygdala" (anterior cortical nucleus and posterolateral cortical nucleus) were identified in the Syrian hamster using injections of 3H-proline into the amygdala followed by light-microscopic autoradiography. The experiments showed that M and C3 belong to a vomeronasal network, composed of the accessory olfactory bulb (AOB) and areas which receive direct projects from the AOB (nucleus of the adcessary olfactory tract, M, C3, and the bed nucleus of the stria terminalis). These areas project almost entirely to one another, forming a circuit with few connections to other brain areas. Exceptions to this were the projections of M to the medial preoptic area (MPOA) and nuclei in the medial basal hypothalamus. These may provide a functionally significant outlet for the telencephalic vomeronasal network in mediating sexual behavior, since lesions of the MPOA have been shown to eliminate male mating behavior in all species of mammals investigated in such experiments. The hypothesis that projections from M to MPOA might mediate chemosensory control of copulation in the male hamster is strengthened by the studies of this behavior after discrete lesions in the amygdala and its efferent pathways. Bilateral lesions of the vomeronasal amygdala in 16 male hamsters resulted in mating-behavior deficits which ranged from a total absence of copulation to apparently normal behavior.

In another study, previously obtained electrophysiological, gas chromatographic, and radioisotope data from bullfrogs suggest that one of the mechanisms underlying olfactory discrimination is the differential sorption of odorants by the mucosal sheet. In the time frame of a sniff this effect would establish different molecular distribution patterns along the mucosa for the molecules of different odorants. Radioactive mapping studies using butyl acetate have been continued. Earlier electrophysiological and gas chromatographic data suggested that butyl acetate would be expected to have a distribution gradient along the mucosa between those of the other two chemicals (octane and butanol). As was true for tritiated octane and tritiated butanol, these butyl actate mapping studies confirm that the molecules of different odorants are indeed distributed in patterns, are predictable from the results of earlier electrophysiological and gas chromatographic experiments. That is, butyl acetate shows a distribution gradient along the mucosa which is less steep than that of butanol but more steep than that of octane. To better define the mucosal sorptive events, a technique using tritiated odorants to measure partition coefficients not only between air and water but also between air and the olfactory mucosa was developed. Mucosal uptake to tritiated butyl acetate is about 1.5 times that of water, indicating that the olfactory mucosa may have an increased ability over water to absorb butyl acetate molecules.

In another study of olfaction it has been shown that in mice the olfactory sensory neurons can be reformed from the stem cells even after total bulbectomy and that their sensory axons can regrow in the spared portions of the forebrain where they form glomeruli and establish synaptic contacts with the local neurons. After partial bulbectomy the regrowing sensory axons from glomeruli in ectopic positions such as the external plexiform layer, the mitral cell layer, and the granule layer. These observations are important in establishing the role of the specific target upon the regrowth of the sensory axons and the adaptability of these axons to unconventional targets. In the absence of the olfactory bulb the olfactory neurons maintain a normal turnover rate and the olfactory marker protein in the neuroepithelium has normal values. The presence of the olfactory bulb does not seem to be essential for the maintenance of maturation of a normal population of olfactory sensory neurons. Failure of the sensory axons to reach any portion of the C.N.S., after bulbectomy because of formation of a scar tissue acting like a dam, results in the formation of large neuromas on the intracranial side of the lamina cribrosa. Under these experimental circumstances the olfactory sensory neurons survive for as long as 12 months; however, the turnover of these neurons is accelerated (the life span of the neurons is reduced to some 15 to 20 days). A very small percent of these neurons (10%) are capable of manufacturing the olfactory marker protein while the others, although provided with a dentrite and an axon, are totally devoid of the specific protein.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1979 through September 30, 1980

UNIVERSITY OF FLORIDA (N01-NS-5-2313)

Title: Study of Auditory Sensitivity in Young Children

Contractor's Project Director: Donald C. Teas, Ph.D.

Current Annual Level of Support: $81,873

Objectives: This contract was awarded to study auditory sensitivity in young children. The goal is the development and evaluation of a battery of tests which can be used to characterize the hearing ability of young children not suspected of having hearing deficits and to examine the feasibility of using such a battery to assess the hearing of infants and young children who are suspected of, or at-risk for, hearing dysfunction. Particular emphasis is being placed on the developmental aspects of the hearing ability of this population.

Major Findings: Three measures (auditory brain responses (ABR), blink-inhibition by acoustic leadtones, and behavioral measures of threshold) are being evaluated with infants, young children and adults. Results show that these measures can be confidently employed to assess auditory sensitivity in the target population of 0-3 year old children. ABR data indicate that changes over time in latency for Wave I are minimal for all stimulus frequencies and may suggest that maturation is complete at the cochlear level for all filtered clicks. This finding is not maintained for Waves III and V which are assumed to occur at higher levels in the brainstem. These data encompass the ages of the same infants from 2 to 60 weeks. The behavioral work has compared threshold measures of 6 and 10--month old infants when the pure tone stimuli are presented via earphones and a loudspeaker. The mean results are not significantly different but the variability is noticeably larger for the earphone presentation. Difficulties continue to be encountered with earphone placement on the infants' small heads. The blink inhibition portion of this project shows that as age increases, inhibition is being replaced by facilitation in the later trials of a test session. Final analyses will account for this finding.

Significance to NINCDS Program and Biomedical Research: Procedures are needed for assessing the hearing of young children who are incapable of providing conventional responses. Without a battery of tests to assess hearing sensitivity at different developmental stages, evaluation of degree of impairment followed by treatment for this population is not possible at the present time.

Cooperating Units: None

Proposed Course of Contract: Data collection will terminate in February 1981 to permit analyses and cross-laboratory comparisons. The final report is due June, 1981 when the contract will be completed.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1979 through December 30, 1979

BOSTON UNIVERSITY MEDICAL CENTER (NO1-HV-5-2971)

Title: Framingham Heart Study - Hearing Assessment of Subjects

Contractor's Project Director: M. Stuart Strong, M.D.

Current Annual Level of Support: $0

Objectives: The goal of this project was to assess the hearing sensitivity of subjects enrolled in the Framingham Heart Study and evaluate any observable relationship between sensorineural hearing loss and cardiovascular status.

Major Findings: Of the 3578 surviving members of the Framingham cohort, 2435 were examined for air and bone conduction hearing thresholds. The prevalence and degree of hearing loss in this population of 58 to 89 year old males and females has been determined. The results are comparable to those obtained in the 1962 survey by the National Center for Health Statistics in the lower frequencies, but are rather divergent for the frequencies from 3 to 6 k Hz. This study also showed that the differential that occurs between male and female patients (females showing significantly better thresholds) through the 70-79 decade is not maintained for patients in the 80-89 decade. Cardiovascular findings have not been analyzed for comparison with the hearing findings due to insufficient funding.

Significance to NINCDS Program and Biomedical Research: This group of subjects should provide a unique opportunity to relate hearing sensitivity and known cardiovascular findings. Vascular disease is known to be associated with some types of hearing losses but these studies have not had access to such a large and well-documented population.

Cooperating Units: National Heart Lung and Blood Institute

Proposed Course of Contract: This amendment to the original NIHLB contract could not be renewed due to a change of policy within that Institute. By the time this decision was made, it was too late to attempt the completion of the additional workscope necessary to perform a comprehensive audiological workup on all patients having measureable hearing loss in the current biennial examination period. Consequently, the proposed work will be attempted after an NINCDS contract is developed for implementation in August 1981 when the next series of examinations is to be initiated. Cardiovascular data will be employed in the analyses of this future work. A TMR will be required in the Spring of 1981.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1979 through September 30, 1980

WAYNE STATE UNIVERSITY (N01-NS-6-2353)

Title: Evaluation of Procedures for Screening Preschool Children for Signs of Impaired Language Development

Contractor's Project Director: Lynn S. Bliss, Ph.D.

Current Annual Level of Support: $0

Objectives:

1) To develop valid language screening procedures for screening preschool children for signs of impaired language development in English, Black dialect and Spanish.

2) To develop reliable instructional materials for training paraprofessionals to administer the language screening procedures.

3) To assess the validity and reliability of the selected screening items, when administered by paraprofessionals to English, Black dialect and Spanish speaking preschool children.

4) To determine whether language impairments are associated with the occurrence of otitis media and/or mild to moderate hearing loss in preschool children.

5) To develop materials for distribution to health and educational service administrators, providing recommendations on how to implement and administer preschool language screening programs.

Major Findings: Nine screening tests were developed; three for Anglo speaking preschool children (one for ages 30 to 36 months, one for ages 37 to 42 months and one for 43 to 48 months); three for preschool children who speak Black dialect between 30 and 36, 37 and 42 and 43 and 48 months; and three for Spanish-American preschool children in the three age groups. Both test sensitivity for detecting language impaired children and the test specificity for not detecting children with normal language development were evaluated. All tests had a sensitivity greater than 85% except for the Spanish-American tests for ages between 30 and 36 and 37 and 42 months. All tests had a specificity of 70% or greater except for the same two Spanish tests. Both the Black dialect and Spanish-American children varied in their degree of difference from Anglo making it difficult to construct a test useful for all children. For example, some Spanish-American children spoke better English than Spanish and few were solely Spanish speaking. Thus, the test for Spanish-American children includes many items in English.

No significant statistical relationship was found between the presence or absence of a speech or language disorder and the presence or absence of otitis media and/or a hearing loss in preschool children who were either Anglo, Black dialect and Spanish speaking.

Significance to NINCDS Program and Biomedical Research: Children impaired in language development cannot progress at the normal rate in school. If such children were detected at preschool age, treatment could begin prior to their entering school. Valid and reliable language screening procedures are needed for conducting early periodic screening for children eligible to receive special assistance under the new Education for the Handicapped Act, P.L. 94-142. This project was designed to meet these needs. The results will provide the procedures, examiner training materials and program organization for conducting preschool language screening.

Cooperating Units: University of Arizona, Tucson, Arizona.

Proposed Course of Contract: The contract was terminated in June 1979 upon successful completion of the work and submission of the final report.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1979 through September 30, 1980

MINNEAPOLIS MEDICAL RESEARCH FOUNDATION, MINNEAPOLIS, MINNESOTA
(N01-NS-7-2378)

Title: A Comprehensive Study of the Language Recovery Process in Adults with Aphasia Following a Cerebrovascular Accident

Contractor's Project Director: Alan B. Rubens, M.D.

Current Annual Level of Support: $117,289

Objectives: The purpose of the research is to develop increased understanding of the neurophysiological and behavioral bases of the language recovery process in aphasic adults, during the first six months following a CVA to determine:

1) The prediction of the outcome of aphasia on the basis of the size and location of brain pathology and neurophysiological activity in each hemisphere;

2) what changes in location and size of brain pathology and neurophysiological activity of either hemisphere, are associated with the degree of language recovery;

3) what changes in behavior are associated with the degree of recovery from aphasia; and,

4) whether patients' verbal learning/memory deficits are associated with prognosis for recovery from aphasia.

Major Findings: All of the experimental testing procedures are now being successfully used in the longitudinal study of aphasic patients during the first six months post CVA. The study period for individual patients has been extended to include repeat examinations at 9 and 12 months since significant behavioral changes have been observed past 6 months. Close to half of the required number of subjects have entered the study with one-third having successfully completed six months of testing on all procedures. The results to date, although only preliminary, have demonstrated significant returns of speech production in some cases with pathology affecting all of the left hemisphere. The results of the blood flow and electrophysiological studies will clarify the relative contribution of right hemisphere in such instances of marked language recovery. The first studies of the inter-relationship between verbal memory functioning and language recovery have demonstrated that patients' verbal memory skills have a significant relationship with the degree of language recovery measured over the first six months.

Significance to NINCDS Program and Biomedical Research: Language recovery in aphasic adults is not well understood. In most cases recovery is rapid during the first nine weeks following the onset of symptoms. The size and location of brain lesions, regional blood flow, and physiological response of each hemisphere during verbal behavior will determine the association between dominant hemisphere status and level of recovery from aphasia. If recovery is not highly associated with changes in the left hemisphere, and the right hemisphere is found to be involved in verbal functioning, both the right and left hemispheres may be involved in language recovery following a CVA. The results will be useful for determining appropriate approaches for treatment.

Cooperating Units: University of Minneapolis Medical Center.

Proposed Course of Contract: During this phase, 60 aphasic adults will be studied during the first six months following the onset of aphasia.

A site visit will be conducted in October 1980 to determine the number of subjects required to provide sufficient data for examining each of the hypotheses statistically. Phase II of the research will be completed when these requirements have been met satisfactorily. Six months will then be required for data analysis and report writing.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1979 through September 30, 1980

UNIVERSITY OF ILLINOIS (N01-NS-7-2380)

Title: Evaluation of a Test of Speech Perception in Noise

Contractor's Project Director: Robert C. Bilger, Ph.D.

Current Annual Level of Support: $121,293

Objectives: The purpose of this contract is to conduct experimental work to determine the inter-list equivalency, performance by signal-to-babble (S/B) functions, and validity of the Speech Perception in Noise (SPIN) Test.

Major Findings: Phase 1 work has been completed with 128 hearing-impaired subjects. It was found that the 10 SPIN lists were not equivalent so an additional Phase of work (Phase 1.5) was initiated and completed to obtain eight equivalent lists. The criteria for equivalency were: (a) the correlation of "obtained scores" with "true scores" for all forms; (b) homogeneity of variance; and (c) equal difficulty. These revised lists have been used in Phase 2 with five sub-groups of subjects (N=90) to evaluate their performance on multiple speech tasks under signal-to-babble ratios (S/B) of 7,4,1 and -2 dB. Other variables included the effect of presence or absence of training in the task and response criteria to a masking paradigm. Analyses of these data are underway.

Significance to NINCDS Program and Biomedical Research: Assessment of suprathreshold speech perception in noise would provide a valuable tool for the practicing clinician in managing hearing-impaired patients. Hopefully, the SPIN Test may also be employed as a predictive measure of the degree of benefit that persons with acquired sensorineural hearing loss may appreciate from a properly selected hearing aid.

Cooperating Units: None

Proposed Course of Contract: An additional Phase (2.5) has been added to the workscope to compare responses by 32 subjects to all eight revised SPIN lists and the 10 revised CHABA sentence lists when presented via earphones. Phase 3 work will follow to determine the validity of the SPIN test as a predictor of how well hearing-impaired listeners use their hearing aids. The addition of Phases 1.5 and 2.5 will necessitate an extension of this contract for one year and a TMR in September 1980.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1979 through September 30, 1980

CHILDREN'S HOSPITAL OF PITTSBURGH (N01-NS-8-2384)

Title: Decongestant/Antihistamine Therapy for Otitis Media with Effusion (OME)

Contractor's Project Director: Charles D. Bluestone, M.D.

Current Annual Level of Support: $0 (Forward Funded in 1979)

Objectives: To determine if the widely-used combination of an antihistamine and a decongestant is effective in the treatment of otitis media with effusion.

Major Findings: Over 400 subjects have been enrolled in this double-blind clinical trial and the attrition rate of 8.2% is below that anticipated. The contractor is enrolling subjects in all designated age groups and will have sufficient numbers for completion as scheduled in FY '81.

Initial analysis of the data by the statistical team was performed and of interest is the apparent strong dependence of cure rate on the duration of OME. Overall cure rate of children with 0-3 week duration of OME is approximately 33% whereas the overall cure rate in children with OME duration of more than 8 weeks is approximately 15%. These data also suggest some dependence of cure on the age of the subject. Overall, the 6-12 years age group demonstrate a 23% cure rate and for the 2 younger age groups the cure rate is approximately 18%.

Significance to NINCDS Program and Biomedical Research: Otitis media is the most common illness seen in the pediatrician's office and despite the routine use of decongestants and/or antihistamines we lack objective evidence of their effectiveness. Otitis media has been a targeted area of research by NINCDS and this work will provide important information on the treatment of otitis media.

Cooperating Units: None

Proposed Course of Contract: With the rate of subject assimilation as anticipated, the projected number of statistical analysis should be reached and all analysis completed, as planned, in July 1981.

Funds for completion of this study have been allocated to the contractor and additional funding is not anticipated for FY '81.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1979 through September 30, 1980

PRESIDENT AND FELLOWS OF HARVARD COLLEGE, CAMBRIDGE, MASSACHUSETTS
NO1-NS-8-2399

Title: Laryngeal Carcinoma: Identification of High Risk Factors

Contractor's Project Director: Kenneth J. Rothman, Dr. P.H.

Current Annual Level of Support: $0

Objectives: To identify those individual health, environmental, and occupational factors which will delineate persons at high risk of laryngeal carcinoma in the United States today. The following objectives will be met:

1. An integration of data available on factors associated with a high risk of laryngeal carcinoma in the United States;

2. an examination of mortality, incidence data and time trends with significantly high rates of laryngeal cancer over the last 10 years; and,

3. complete investigations of occupational factors in counties where incidence or mortality is greater than in the general population.

Major Findings: An integration of the data available on the epidemiology of laryngeal carcinoma demonstrated that occupational factors have not been well studied independent of smoking and alcohol consumption, except for asbestos which can be considered a strong risk factor.

Case control studies have been designed to study the possible contribution of other occupational exposures such as wood dust, nickel, mustard gas, grease and oil, isopropyl alcohol, leather, paper, chemical and textiles. Four hospitals in Augusta, Georgia and three hospitals in New Haven, Connecticut have agreed to participate in a case control interview study of laryngeal carcinoma. Over 160 cases and 400 controls will be included. Both smoking and alcohol consumption will be controlled while occupational exposures will be examined in detail.

Significance to NINCDS Program and Biomedical Research: The chances of survival following laryngeal carcinoma can be significantly enhanced with early treatment and the vocal mechanism may be spared when surgical intervention is not necessary. Screening programs are needed of persons at high risk of laryngeal cancer (such as industrial male workers who are heavy smokers and drinkers between 60 and 65 years of age). Before such programs can be initiated, a clearer understanding is needed of what factors could delineate persons at high risk for this disease. The final report of this project will indicate what further research is needed for delineating persons who are at high risk as well as what is currently known about the relative risk for this disease in various sections of the population.

Cooperating Units: The National Cancer Institute, Office of Biometry, four Richmond County, Georgia hospitals (Georgia Regional Hospital, Medical College of Georgia Hospital, St. Joseph Hospital and University Hospital) Yale-New Haven Hospital and St. Raphael Hospital, New Haven Connecticut.

Proposed Course of Contract: Both Phase II and III of the research have been initiated. The contract is expected to terminate in December 1981.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1979 through September 30, 1980

UNIVERSITY OF NORTH CAROLINA, CHAPEL HILL, NORTH CAROLINA (N01-NS-9-2305)

Title: The Acquisition of Language and Communicative Skills by Speech and Sign in Infantile Autism

Contractor's Project Director: Thomas Layton, Ph.D.

Current Annual Level of Support: $238,164

Objectives: To conduct an experimental study of the development of communicative skills by autistic children when training involves only speech stimuli, only sign stimuli, speech and sign stimuli presented simultaneously, or speech and sign presented independently. The research will determine after six months of training which method of language training results in: Greater expressive and receptive language skills; greater use of language skills for communication; and greater retention of language skills following training. The study will also determine whether autistic children evidence cross-modality transfer of information learned in speech or sign to the other modality; whether simultaneous presentation of stimuli in two different modalities interferes with learning; and whether autistic children show similar language learning difficulties in both the speech and sign modalities.

Major Findings: During this year, the staff has successfully developed language training manuals for teaching autistic children sign production and comprehension. Comparable manuals for teaching equivalent language through speech alone and speech and sign combined have also been developed for the research. Training procedures, prelinguistic shaping, subject selection, response recording forms and final evaluations have been successfully developed for the experimental study and an adequate number of children located for the research. Work on the experimental study began in September 1980.

Significance to NINCDS Program and Biomedical Research: Impaired speech and language development is common to all children with infantile autism although the degree of impairment varies among children. The etiology of these disorders is not known and the bases for these children's specific difficulties in learning language is not well understood. Some have proposed auditory and speech processing difficulties which could account for these impairments. Recently, there have been clinical reports of marked success with some of these children in learning language using signs or gestures and reports that once such children begin to use signs to communicate they may vocalize spontaneously and develop speech for communication more readily. This research will examine these issues experimentally and have significance for the development of improved speech and language training for autistic children.

Cooperating Units: None

Proposed Course of Contract: The work for Phase II will require two years. The final phase, involving data analysis and report writing, will run six months and should be complete in December 1982.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1979 through September 30, 1980

UNIVERSITY OF CALIFORNIA, SAN DIEGO (N01-NS-9-2322)

Title: Evaluation of the Outcome of Preschool Impairment in Language Development.

Contractor's Project Director: Paula Tallal, Ph.D.

Current Annual Level of Support: $0 (Forward Funded in FY 1979)

Objectives: To determine, through a longitudinal intensive study, the outcome of preschool impairments in language development. In particular, the research will determine:

1) Whether the patterns of development of language, speech, listening and learning skills found in four year old language impaired children differ from those of normal children when both groups are examined annually between 4 and 9 years of age;

2) whether preschool children impaired in language development have greater difficulties in acquiring reading and writing skills than normal children at 6,7,8 and 9 years of age;

3) whether preschool children impaired in language development are impaired in their verbal learning, memory and scholastic achievement in comparison with normal children at 5,6,7,8 and 9 years of age;

4) whether certain familial and language, speech, listening and learning characteristics of language impaired children at four years of age, are predictive of their language, reading, writing and scholastic abilities at 5,6,7,8 and 9 years of age.

Major Findings: During the first year, work has progressed on the developmental phase of the research. A multidisciplinary team has provided consultation for the development of measurement tools including: receptive tests of syntactic, morphology and semantic language development; reading comprehension and skills acquisition; verbal learning and memory skills; social maturity; recognition and free recall of story telling; math skills; speech perception and speech production; and scholastic achievement. The location of subjects for the research has begun and adequate numbers of the language impaired (N = 100) and normal controls (N = 105) subjects are available.

Significance to NINCDS Program and Biomedical Research: The research will provide critically needed information for clinical treatment and planning for language disorders. It will be determined whether language impaired children differ from normal children in their language acquisition or whether they are simply delayed in their development of the normal sequence of language acquisition. Present treatment procedures are based on the normal language development process. It is likely that this is inappropriate but until information is obtained on language development in the language impaired population, more appropriate methods cannot be developed.

The research will determine whether preschool impairments in language development are precursors of difficulties in learning to read and write. The research will provide a detailed analysis of the types of difficulties these children have when learning to read. With improved understanding of the reading deficits of children who have a linguistic difficulty, remedial procedures for this segment of the reading disabled population can be improved.

Cooperating Units: Children's Hospital and Health Center, San Diego

Proposed Course of Contract: A contract was awarded for the first three years to include the developmental phase, subject selection and the first eighteen months of the longitudinal study. A Technical Merit Review site visit will be held in the third year to review the study procedures before extending the contract for the final four years of the study.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1979 through September 30, 1980

UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT SAN ANTONIO (N01-NS-0-2328)

Title: Efficacy of Adenoidectomy/Tympanostomy Tubes for Persistent Otitis Media with Effusion.

Contractor's Project Director: George A. Gates, M.D.

Current Annual Level of Support: $364,442

Objectives: To determine if the widely performed procedures tympanostomy tube insertion and/or adenoidectomy are effective in the treatment of otitis media with effusion.

Major Findings: As this contract was awarded in February 1980 no substantive data has yet been analysed. The physical facilities of the "Otitis Media Study Center" located in the Santa Rosa Medical Center Outpatient Clinic have been established and the project team has entered subjects into the pilot phase. Few logistical problems have been encountered and the project is progressing quite smoothly. All project personnel have been hired and the project management appears to be very good.

Significance to NINCDS Program and Biomedical Research: Otitis media is the most common illness of the pediatric age group and surgical treatment is very commonly recommended for patients failing medical therapy. Despite this frequency we lack objective evidence of the efficacy of these procedures. Otitis media has been a targeted area of research by NINCDS and this work will provide important information on the treatment of otitis media.

Cooperating Units: None

Proposed Course of Contract: The project is expected to cover 5 years with completion in February 1985. Technical Merit Review will be done after year 3.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
March 31, 1980 through September 30, 1980

PURDUE UNIVERSITY (NO1-NS-0-2329)

Title: Determination of Effects of Hearing Aid Amplification on Children

Contractor's Project Director: Carl A. Binnie, Ph.D.

Current Annual Level of Support: $151,582

Objectives: To determine whether hearing aid amplification significantly affects the residual hearing of the groups of children under study and if a relative threshold shift (comparison of pure tone threshold shift over time between the aided and unaided ears) relates in a significant manner to: (a) the electroacoustic characteristics of the hearing aid; (b) the amount of hearing aid usage in hours per week and number of months and/or years; (c) the degree of hearing loss when the aid was introduced; (d) the earmold or coupling system used with the hearing aid; (e) specific or nonspecific etiological information; and (f) progressive hearing deterioration.

Major Findings: With the recent initiation of this contract, the project team has been involved in assembling the necessary instrumentation, enrolling subjects for the study and conducting a pilot study with adult subjects.

Significance to NINCDS Program and Biomedical Research: The National Research Strategy identified the following goal #67 which this project addresses: The special needs of the pediatric and aging populations should be considered from the viewpoint of sensory aids and habilitation/rehabilitation processes.

Cooperating Units: Indiana School for the Deaf; Indiana University School of Medicine; Home Hospital in Lafayette, Indiana; and St. Elizabeth Hospital in Lafayette, Indiana.

Proposed Course of Contract: Hearing thresholds of hearing-impaired children and normal hearing children will be obtained to determine the reliability and efficiency of psychophysical and electrophysiological methods of measurement. In addition, frequency selectivity measures will be made to determine temporary cochlear changes resulting from amplification. Data collection and analyses are expected to be completed in three years.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1979 through September 30, 1980

SYRACUSE UNIVERSITY, SYRACUSE, NEW YORK (N01-NS-0-2331)

Title: Methods for Studying Phonatory and Articulatory Control in Young Children Who Stutter

Contractor's Project Director: Edward Conture, Ph.D.

Current Annual Level of Support: $225,550

Objectives: 1) To develop measurement techniques and testing procedures for assessing the speech production skills of young children between 4 and 6 years of age which are noninvasive, objective and reliable. 2) To determine which aspects of phonatory and articulatory control during speech production differ in fluent and stuttering children between 4 and 6 years of age.

Major Findings: None as yet, contract was initiated July 28, 1980.

Significance to NINCDS Program and Biomedical Research: There is a critical need to stimulate research on stuttering; NINCDS is the prime BID within the U.S. government for the support of stuttering research and only supports two grants in this area. Recent research on adults has indicated some differences in phonatory control between normal and stuttering adults. Research projects need to examine the hypothesis of whether or not children who become persistent stutterers show differences in phonatory control during the normal developmental period of non-fluency.

Objective methods of assessing speech timing control in young children who stutter will provide the necessary tools for research on the development of stuttering in young children. These methods of assessment may lead the way to early identification of young children who are at risk of developing speech dysfluencies and indicate appropriate intervention techniques for improving the development of speech timing control and preventing stuttering.

Cooperating Units: None

Proposed Course of Contract: Once the development of the measurement techniques and speech tasks during Phase I is complete and approved by the NINCDS Project Officer, the experimental phase will begin. Phase I will require 2 years for completion while Phase II will require 1 year. The contract is expected to terminate in July 1983.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02185-06 CDP

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Characteristics of Dysarthric Speech Associated with Neurologic Disease

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.	C.L. Ludlow, Speech Pathologist, CDP, NINCDS
	C.B. Cardano, Speech Pathologist, CDP, NINCDS
	R. Polinsky, Neurologist, LCS, NIMH

COOPERATING UNITS (if any)

LCS, NIMH

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.35	.25	.10

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The long-range goal is to develop objective assessment procedures and measurement tools for assessing speech motor control disorders exhibited by dysarthric patients with neuromotor diseases/disorders. Both the degree of speech dysfunction and the profile of the type of speech disturbances are of interest. Using many different measures, discriminant function analyses were used to select profiles of measures for assessing each type of dysarthria which differentiate patients from normal controls as well as discriminate accurately between different types of speech disturbances such as: hypokinesia in Parkinson's disease, Shy Drager syndrome, Tardive Dyskinesia and Huntington's Chorea. These measurement profiles include such attributes as speech intensity, fundamental frequency, perturbation, voicing errors, rate control, latency of labial movement and laryngeal abduction. These profiles provide objective procedures which are critically needed for clinical assessment of different types of dysarthria and identify those aspects of speech motor control which should be focused on during treatment of each particular disorder.

Project Description

Objectives:

1) To determine which measures of speech motor control are useful in the early identification of bucco-facial disturbance in Tardive Dyskinesia.

2) To determine which measures of speech motor control will be useful in the early diagnosis of Shy Drager syndrome and will differentiate between patients with idiopathic orthostatic hypotension and those with Shy Dragers disease.

3) To determine which measures of speech motor control are indicative of early stages of Huntington's chorea and are valid indicators of degree of disease progression.

Methods Employed: All patients are tested in a sound controlled environment with intensity and frequency calibration using an acoustic microphone, accelerometer, contact microphone and laryngograph. Acoustic analysis of phonatory frequency, intensity and perturbation, articulatory timing and formant structure are conducted with a sound spectrograph, graphic level recorder, and a pitch tracking microprocessor. Measures are made with a small laboratory computer and an x-y digitizer and microprocessor. The acoustic analyses and measurements are made without knowledge of the speakers identity and drug-placebo state. The reliability of all measures is greater than .90. Measures are assessed statistically for degree of independence and variables are selected which are independent measures of speech motor control attributes and have significant weights in the discriminant functions for differentiating patients from controls and between different types of dysarthria. Twenty-eight measures have qualified and can be classified as independent measures of the following attributes: speech rate control; control of complex articulation; voicing control; fundamental frequency control; control of speech segment timing; and control of speech intensity.

Subjects: All patients and normal aging controls are recorded in a placebo state at least twice to eliminate practice effects. Some patients are participating in double-blind crossover drug-placebo studies and are recorded at least twice in each condition.

Major Findings:

1) The profile of speech disturbance in bucco-facial tardive dyskinesia is reduced range in fundamental frequency, reduced rate of laryngeal abduction and adduction during vowel repetition, reduced rate of speech articulation, and reduced range in speech intensity.

2) The profile of speech disturbance in hypokinesia in Parkinson's disease is severely reduced laryngeal abduction during vowel repetition, reduced range in speech intensity, limited duration of phonation, reduced rate control during speech articulation, and increased latency of tongue movement for

speech articulation.

3) During the early stages of Shy Drager syndrome, rate of laryngeal abduction and latency of speech articulation will differentiate these patients from normal controls and patients with idiopathic orthostatic hypotension. During later stages of Shy Drager syndrome, measures of pitch perturbation in phonation and waver accurately discriminate such patients from normal aging controls and from patients with hypokinesia in Parkinson's disease.

Significance to NINCDS and Biomedical Research: The development of objective procedures for the assessment and differential diagnosis of various types of dysarthria in adults with neurological diseases, will enable researchers and clinicians to evaluate different treatments for these patients. The information being gained on which speech production processes are particularly impaired in each of the neurological diseases, will contribute to our understanding of both normal and disordered speech production as well as providing directions for treatment.

Proposed Course of Project: The following presentations made at scientific meetings during the last year are currently being written for publication. One has been submitted for publication.

-Cardano, C.B. and Polinsky, R.J. "Speech symptoms associated with early signs of Shy Drager Syndrome." Annual convention of the American Speech-Language-Hearing Association, Atlanta, GA, November 1979.

-Ludlow, C.L., Coulter, D. and Cardano, C. "Application of pitch perturbation measures to the assessment of hoarseness in Parkinson's disease." Annual meeting of the Acoustical Society of America, Salt Lake City, Utah, November 1979.

-Coulter, D., Ludlow, C. and Gentges, F. "Determination of lower limits of pitch variation in normal larynges." Annual meeting of the Acoustical Society of America, Salt Lake City, Utah, November 1979.

-Ludlow, C.L., Hanson, D.G., Williams, A., Cardano, C.B. and Coulter, D. "Laryngeal involvement in Shy Drager syndrome." Meeting of the Association for Research in Otolaryngology, St. Petersburg Beach, Florida January 1980.

Testing of patients and individuals at high risk for Huntington's chorea will be completed in November 1980.

Publications:

Ludlow, C. and Bassich, C. The differential diagnosis of syndromes of dysarthria using acoustic measures. In Lass, N. (Ed.), Speech and Language: Research and Theory, Volume 5, New York, Academic Press, Inc., 1981, in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02247-04 CDP

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

The Characteristics and Treatment of Vocal Tics and Language Processing in Gilles de la Tourette's Syndrome

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.	C.L. Ludlow, Speech Pathologist, CDP, NINCDS
Other:	M.H. Ebert, Chief, Section on Experimental Therapeutics, IR, NIMH
	C.B. Cardano, Speech Pathologist, CDP, NINCDS
	R. Polinsky, Neurologist, LCS, NIMH

COOPERATING UNITS (if any)

IR, NIMH

LAB/BRANCH

Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .35	PROFESSIONAL: .25	OTHER: .10

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A series of research studies are being conducted to determine the following:

1) The characteristics of vocal tic phenomena in Gilles de la Tourette's Syndrome.

2) To determine the differential effects of various neuropharmacological treatments on the type and severity of vocal tics in patients with Gilles de la Tourette's Syndrome.

3) The relationship of vocal tic production to propositional language behavior and speech fluency.

4) Whether history of tics, Tourette Syndrome or stuttering in patients' family history are predictive of the vocal tic and language dysfunctions seen in patients with Tourette syndrome.

Project Description

Objectives: To determine: the characteristics of Gilles de la Tourette (GT) syndrome; the relationships between various vocal tic symptomatology in GT; the relationship of language processing deficits to vocal and motor tic symptomatology in GT; the differential characteristics of speech dysfluency in GT from stuttering; the predictive relationship of familial history with the severity and type of vocal tic and language processing deficits in GT syndrome; and, the efficacy of various neuropharmacological agents in the treatment of GT.

Procedures: Calibrated speech recordings are made in a sound controlled environment. Oscillographic tracings are used to measure pause durations in connected speech and the place of occurrence of vocal tics relative to speech onset. Language processing skills are assessed using a standardized battery as well as an experimental battery assessing rate of nominative retrieval, recall of nominative material presented by speech, in writing and pictorally, and comprehension of complex directions presented by speech, in writing or by gesture. Laterality of speech perception during dichotic listening is assessed using minimal pair contrasts of CV syllables. Reading skills are assessed using the Gates-McKillop Diagnostic Battery. All tests are scored without knowledge of the subjects identity (GT or age and sex matched control) or placebo-drug state (Placebo, Haloperidol or Lecithin).

Subjects: Subjects are seen on an outpatient basis following diagnosis of GT syndrome according to Shapiro's five criteria. Initial speech and language assessment are done after patients have been off all medications for at least two weeks. Only those admitted as inpatients are retested twice weekly during drug-placebo double blind cross-over studies.

Major Findings:

1) Language processing, reading and nominative retrieval deficits occur in 60% of patients with GT and are most prominent during adolescence and in at ientsia.

2) Vocal tics follow a progression from the least verbal (laryngeal, labial, lingual and respiratory tics) forms appearing first and most frequently and with the more verbal tics appearing later and in more severe forms of the disorder (speech sounds, coprolalia, jargon and pallilalia).

3) Lecithin is not as effective as haloperidol in reducing vocal tics in GT. Although lecithin significantly reduced vocal tics without side effects in some individuals it significantly increased tics in a few GT patients.

4) During speech production without vocal tics, GT patients have pauses prior to speech initiation significantly greater than normal controls. The distribution of these pauses before phrase production indicates that a language formulation disorder affects speech encoding in these patients and is distinct from speech dysfluency seen in stuttering.

Significance to NINCDS and Biomedical Research:

This research has both basic and applied significance for the understanding and treatment of this syndrome. First, the demonstration of a language performance deficit associated with vocal tic symptomatology indicates either that the pathology involves more than basal ganglia mechanisms or that the pathology involving the basal ganglia has an effect on cortical functioning in more severe cases of this syndrome. Second, the demonstration of a continuum of vocal tic symptomatology provides a scale by which the severity of syndrome involvement can be assessed in patients with different symptoms. Finally, the study of individuals' responses to acute neuropharmacological manipulations provides information on the possible biochemical bases for this syndrome.

Proposed Course of Project: During this year, over 50 patients with GT syndrome ranging in age from 5 to 65 years and age and sex matched normal controls have completed speech and language testing. Scoring of language test performance and analysis of vocal tic symptomatology is complete and undergoing statistical analysis. Papers are currently being drafted for submission for publication.

Publications:

Polinsky, R.J., Ebert, M.H., Caine, E.D., Ludlow, C.L. and Bassich, C.J. Cholinergic treatment in the Tourette syndrome. The New England Journal of Medicine, Vol. 302(23): 1310, 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02336-03 CDP

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Early Identification of Drug-Induced Ototoxicity

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. E. Elkins, Audiologist, CDP, NINCDS
Other: A. Pikus, Audiologist, CC
A. Grimes, Audiologist, CC

COOPERATING UNITS (if any)
Radiation Oncology Branch, NCI
Division of Cancer Treatment, NCI
Clinical Center, NIH

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.30	.30	.00

CHECK APPROPRIATE BOX(ES)
☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Certain pharmaceutical agents used in the treatment of cancer are known to have toxic effects upon the hearing of patients. Cochlear damage is manifest by a high-frequency hearing loss and general difficulty in understanding normal speech conversation. Periodic assessment of pure tone thresholds and suprathreshold speech perception are being conducted to evaluate and relate degree and progression of ototoxicity to drug dosage and frequency of administration.

Project Description:

Objectives: To develop techniques for the assessment of ototoxicity related to the administration of certain chemotherapeutic agents employed in cancer treatment. The following areas are being addressed: a) type of hearing loss, b) onset and degree of loss relative to dosage and preexisting hearing condition, c) documentation of onset of tinnitus and/or vertigo, d) predisposition to ototoxic effects, e) unilateral/bilateral symmetrical loss f) suprathreshold speech perception, g) prediction of probable ototoxicity, and h) possible reversibility of ototoxic effects.

Methods Employed: In addition to routine procedures, monosyllabic words and sentence stimuli are presented at various signal-to-noise ratios (S/N) and at different levels above puretone or speech reception threshold levels.

Major Findings: Phase II data collection is continuing with a selected group of subjects. Lack of constant referral by the attending physicians has slowed progress this year. In addition, documentation of drug dosages has not always been complete so a number of patients evaluated have not been entered into the data analyses due to incomplete information. It is essential that all variations of the experimental drugs be identified along with the dosage and frequency of administration.

Significance to NINCDS and Biomedical Research: The development of repeatable and valid methods of assessing hearing impairment following the administration of known drug dosages would provide the clinician with documentation for the managing physicians who in turn may reassess their drug protocols. A reliable method of predicting ototoxicity is definitely needed if prevention of impairment is to be realized.

Proposed Course of Project: Further investigation will be given to the problems and procedures identified above with a patient population available through cooperation with the National Cancer Institute.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02337-03 CDP

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

The Effects of Stimulants on the Auditory Processing and Language Skills of Hyperactive, Language Impaired and Normal Subjects.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. C.L. Ludlow, Speech Pathologist, CDP, NINCDS
Other: J.L. Rappaport, Psychiatrist, IR, NIMH
G.L. Brown, Psychiatrist, IR, NIMH
C.B. Cardano, Speech Pathologist, CDP, NINCDS

COOPERATING UNITS (if any)

IR, NIMH

LAB/BRANCH

Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.50	.25	.25

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A series of studies are being conducted to determine the following:

1) Whether the effects of stimulants, including dextroamphetamine and caffeine, on language production and speech fluency are similar in normal adults, normal boys, hyperactive boys and language impaired boys.

2) Whether auditory processing disorders occur in hyperactive boys who are without disorders in speech, language and reading.

3) Whether auditory processing skills in young adults are affected by the administration of dextroamphetamine.

4) Whether auditory processing disorders in hyperactive boys with and without disorders in speech, language and reading respond similarly to the administration of dextroamphetamine.

Project Description

Objectives: To determine:

1) Whether dextroamphetamine has a beneficial effect on the auditory processing skills of normal adults;

2) whether caffeine has similar effects to dextroamphetamine on the language processing and speech fluency behaviors of normal and hyperactive boys;

3) whether hyperactive boys who have normal speech, language and reading skills, have auditory processing deficits similar to those found in language impaired populations;

4) whether dextroamphetamine similarly affects auditory processing skills in language impaired hyperactive boys and hyperactive boys who are without speech, language or reading disorders.

Procedures: On admission to the study each subject receives a complete battery of standardized tests of speech, language, reading, intelligence and behavior by a multidisciplinary team.

Modular programming equipment is used to program the administration of acoustic stimuli, record subjects responses and their reaction times during four auditory processing experiments assessing threshold in noise, vigilance, mean reaction time, gap detection and temporal order processing (after Hirsh and Sherrick).

Speech production is recorded during a communication barrier game in which subjects must direct a listener on how to construct block designs without visual feedback. All speech production is transcribed and the rate of speech production (words/min.), and the number of dysfluencies between and within words are tabulated.

All subject testing and data analysis is performed without knowledge of drug-placebo condition. Experiments involving dextroamphetamine and caffeine involve different subjects and both are double-blind counter-balanced crossover trials of drug and placebo conditions.

Major Findings:

1) Hyperactive boys who are without speech, language and reading difficulties were found to have auditory processing deficits similar to those that occur in language impaired populations. This finding brings into question the assumption that auditory processing deficits are the basis for, or contribute to, the language disorders of language impaired patients.

2) The stimulants caffeine and dextroamphetamine have been found to have different effects on speech and language in normal adults. Caffeine administration resulted in increased speech rate and rate of naming while dextroamphetamine increased speech fluency, the amount which subjects talk,

but did not alter their speech rate. Since these agents have differential effects on speech and language production, they have potential for improving different speech and language disorders.

3) Dextroamphetamine was found to enhance the auditory processing skills of normal adults. Both temporal order perception and mean reaction time were significantly enhanced. However, the more simple tasks of threshold detection in noise and gap detection were not altered with drug administration indicating that the effects of dextroamphetamine on auditory function are more centrally based.

4) Dextroamphetamine significantly improved the auditory processing deficits of hyperactive boys who were without deficits in language, speech or reading. With administration of dextroamphetamine, the auditory processing skills of these subjects became similar to normal. In comparison, when language impaired hyperactive subjects, who had similar auditory processing deficits in the placebo condition, were administered dextroamphetamine they did not become similar to normal in their auditory skills although they did improve to a significant degree. Thus although both groups had significant auditory processing deficits in comparison with normal controls in the placebo condition, the effects of stimulant drug treatment were greater in the hyperactive group without language, speech or reading deficits.

Significance to NINCDS Program and Biomedical Research: Recently a great deal of attention has focused on the auditory processing deficits of language impaired children and adults. Training programs aimed at improving these skills in language impaired children are now prolific and are based on the assumption that such deficits are either the basis of or contribute to the language disorder in such children. The finding that such auditory processing disorders exist in children who are without deficits in reading, language or speech brings this assumption into question. Rather, such deficits may be a more general sign of many different types of cognitive disorders.

The differential effects of dextroamphetamine on auditory processing disorders in two groups of hyperactive children indicate that the neurological bases for these disorders may differ between language impaired and non-language impaired hyperactive boys.

Proposed Course of Project: Subject testing is close to complete. The following presentations were made at scientific meetings during the last year and are currently being written for publication. One has been submitted for publication.

-Ludlow, C.L., Richards-Munn, B. and Cullison, B.L. "Drug effects on the communicative abilities of hyperactive and normal children." Annual meeting of the American Speech-Language-Hearing Association, Atlanta, GA, November, 1979.

-Ludlow, C.L., Caine, E., Cudahy, E. and Cardano, C. "Effects of neuropharmacological agents on auditory processing skills in young adults." Annual meeting of the Acoustical Society of America, Salt Lake City, Utah, November 1979.

-Ludlow, C.L., Cardano, C.B., Brown, G.L. and Cudahy, E. "Effects of dextroamphetamine on auditory perceptual skills in hyperactive boys." Annual meeting of the International Neuropsychological Society, January 1980.

Publications:

Ludlow, C.L., Rappaport, J.L., Bassich, C. and Mikkelsen, E.J. Differential effects of dextroamphetamine on language performance in hyperactive and normal boys. In R.M. Knights and D.J. Bakker (Eds.), Treatment of Hyperactive and Learning Disordered Children: Current Research. Baltimore: University Park Press, 1980.

Rappaport, J.L., Buchsbaum, M.S., Weingartner, H., Zahn, T., Ludlow, C., Mikkelsen, E., Langer, D., Bunney, W.E. Dextroamphetamine: Cognitive and behavioral effects in normal and hyperactive children and normal adults. Archives of General Psychiatry, 1980, in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02395-02 CDP

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Analysis of Fluctuating Hearing Loss Associated with Cogan's Syndrome

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. A. Pikus, Audiologist, CC
Other: B.F. Haynes, LCI, NIAID
E. Elkins, Audiologist, CDP, NINCDS

COOPERATING UNITS (if any)
Clinical Center, NIH
Laboratory of Clinical Investigation, NIAID

LAB/BRANCH
Communicative Disorders Program, NINCDS

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .10	PROFESSIONAL: .10	OTHER: .00

CHECK APPROPRIATE BOX(ES)
☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

To assess the course of the auditory deficit associated with Cogan's Syndrome. Six patients have been audiologically evaluated following treatment with corticosteroids and/or diuretic therapy.

Project Description:

Objectives: To develop accurate audiologic indices of the pattern of hearing deficit in Cogan's Syndrome and to document relationship of hearing deficit to therapy.

Methods Employed: Standard audiologic test battery is utilized weekly or biweekly including middle ear analysis. Special auditory tests are repeated intermittently to verify the cochlear nature of the auditory effects of this disease process.

Major Findings: All six patients have presented with interstitial keratitis, vertigo, tinnitus and sensorineural hearing loss. Following corticosteroid treatment, all subjects showed an initial improvement in hearing for pure tones and speech. Subsequent fluctuations in hearing were unresponsive to corticosteroids. Appropriate case management for these patients is under development.

Significance to NINCDS and Biomedical Research: The development of an audiological profile of subjects with Cogan's Syndrome should provide clinicians with information for successful management of these patients.

Proposed Course of Project: Continued investigation of additional Cogan's Syndrome patients will be carried out through cooperation with the National Institute of Allergy and Infectious Diseases and the National Eye Institute.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02396-02 CDP

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Auditory Deficits in Osteogenesis Imperfecta**

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. : J. R. Shapiro, CC, NIH

Other: A. Pikus, Audiologist, CC, NIH
E. Elkins, Audiologist, CDP, NINCDS
R. Ulvestad, Otolaryngologist, CDP, NINCDS
E. Gross, Chief, Molecular Structure Section, ERRB, NICHD
J. W. Hansen, Pediatrician, Developmental Biology & Clinical Nutrition Section, NPMB, NICHD
S. Levin, Dept. of Otolaryngology, Johns Hopkins University
K. Rosenbaum, Dept. of Genetics, Children's Hospital, Washington, D.C.
D. Rowe, Dept. of Pediatrics, University of Connecticut

COOPERATING UNITS (if any)
LDBA, NIDR; CC, NIH; Molecular Structure Section, ERRB, NICHD; Developmental Biology & Clinical Nutrition Section, NPMB, NICHD; Johns Hopkins University; University of Connecticut; Children's Hospital, Washington, D.C.

LAB/BRANCH
Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .20	PROFESSIONAL: .20	OTHER: .00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Methods are being developed to delineate the types of hearing losses associated with Osteogenesis Imperfecta (OI). Measurement of middle ear function by tympanometry and acoustic reflexes are being employed to classify patient responses in conjunction with new collagen classifications.

**[This study is the CC/NINCDS portion of a larger study entitled: COLLAGEN METABOLISM IN OSTEOGENESIS IMPERFECTA (OI).]

Project Description:

Objectives: This study evaluates all OI patients for audiologic abnormalities, using the standard threshold and suprathreshold techniques with special emphasis on middle ear analysis, in an effort to classify the different kinds and severity of hearing loss and perhaps identify carrier status in certain types as well as middle ear factors related to prognosis for future audiologic deficit. Complete families of patients are now being evaluated as well.

Methods Employed: Routine audiologic battery: consisting of threshold puretone and speech measurements; suprathreshold discrimination for speech testing; tolerance levels for speech under headphones (UCL); tympanometry and the measurement of contralateral acoustic reflexes. Special auditory tests are administered as indicated.

Major Findings: The peripheral auditory deficits associated with OI have been studied in over 100 patients and family members with a special emphasis on middle ear function analysis. A significant number of patients and presumably-non-affected family members have demonstrated specific abnormalities in tympanometry and acoustic reflex measurements. The patterns of these findings with concurrent biochemical evidence suggest a need to re-evaluate the mode(s) of inheritance in OI.

Significance to NINCDS and Biomedical Research: Identification of carrier status in OI by means of an easily administered audiologic evaluation would have great value in the management of families in which OI is prominent.

Proposed Course of Project: This project is ongoing and will continue to assess the parameters mentioned above.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02440-01 CDP

PERIOD COVERED

October 1, 1979 through September 30, 1980

TITLE OF PROJECT (80 characters or less)

The Development of Acoustic Measurement Tools for Assessing Vocal Pathology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. C.L. Ludlow, Speech Pathologist, CDP, NINCDS
Other: R. Naunton, Director, CDP, NINCDS
D. Coulter, Speech Scientist
F. Gentges, Computer Programmer and Software
F. Stucker, National Naval Medical Center
R. Eldridge, IRP, NINCDS

COOPERATING UNITS (if any)

IRP, NINCDS and National Naval Medical Center

LAB/BRANCH

Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.50	.25	.25

CHECK APPROPRIATE BOX(ES)

X (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose is to determine the sensitivity of various acoustic measures to vocal pathology associated with laryngeal diseases/disorders including laryngeal carcinoma, vocal polyps, vocal nodules and contact ulcers. Acoustic assessment procedures will provide an objective means of quantifying voice disorders or dysfunctions, and evaluating the effects of various treatments on vocal pathologies.

A microprocessor has been developed for quantifying frequency perturbation (jitter) while a similar system has been developed for quantifying amplitude perturbation (shimmer). Both measurement techniques have 6 to 10 times improved resolution over previous methods of measurement, and provide indices of vocal function which are stable across normal adults with different fundamental frequencies.

Project Description

Objectives: To determine whether measures of frequency perturbation and amplitude perturbation and various processing algorithms can be developed which will:

1. Accurately identify patients with early signs of laryngeal disease and discriminate them from normal adults of the same age and sex;

2. assess the degree of vocal dysfunction in various forms of laryngeal pathology;

3. relate to the size and location of laryngeal pathology;

4. relate to perceptual judgements of degree of vocal dysfunction;

5. accurately reflect changes in vocal function following successful treatment of vocal nodules and polyps.

Procedures: Both patients and normal volunteers receive the following examinations: indirect laryngoscopy; an extensive medical history on laryngeal and respiratory health, smoking, drinking and vocal abuse; and speech recording with acoustic and throat contact microphones; and examination with an accelerometer and a laryngograph. Recordings are analyzed through microprocessors which filter and select glottal periods and peaks for measuring individual cycle lengths and amplitudes. The resulting signals are digitized and further processed using measurement algorithms on a dedicated laboratory computer.

Three speech pathologists have been trained over a three month period to judge extended phonations on twelve different attributes of pitch, loudness and quality. Intra-class correlation coefficients for all judgements are greater than .90.

Subjects: Diagnosed cases of vocal pathology due to neoplastic growths on the larynx including carcinoma, polyps, nodules or contact ulcers, and normal volunteers of the same age and sex characteristics are being studied at the NIH as outpatients. Normal volunteers comprise two groups: one group includes a random selection of normal volunteers with histories of smoking and/or drinking; the second group are active members of the Mormon Church who neither smoke nor drink.

Major Findings: Microprocessors for quantifying frequency and amplitude perturbation have been developed. A comparative study of frequency perturbation values measured by the new microprocessor approach and those reported using digital processing demonstrated a resolution eight times improved over previous approaches and that the computation of Jitter Ratios yielded an index of vocal function which is stable across normal speakers regardless of differences in fundamental frequency.

Significance to NINCDS and Biomedical Research: Objective procedures are needed for measuring vocal function in patients with laryngeal pathology. Such procedures are needed for non-invasive mass screening of individuals at high risk for laryngeal pathology. Those individuals found to have early signs of vocal pathology would then be referred to an otolaryngologist for a laryngeal examination.

Objective measurement procedures are needed for the assessment and re-evaluation of patients with laryngeal pathology. Such measures of vocal pathology will provide methods for evaluating the adequacy of patients' laryngeal function for phonation. At present, only perceptual judgements of the otolaryngologist and/or speech pathologist are available for evaluating the effects of treatment or degree of pathology in phonatory functioning.

Proposed Course of Project: Patient testing should be complete by February 1981. At the same time, work is progressing on further refinement of the jitter and shimmer microprocessor and the development of measurement algorithms for independent assessment of the following attributes of vocal function: cycle length deviation from linear trend; cycle amplitude deviation from linear trend; change in cycle length over time (slew); number of peaks in slew over time; change in amplitude over time; and number of peaks in amplitude over time.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02441-01 CDP

PERIOD COVERED

April 1, 1980 - September 30, 1980

TITLE OF PROJECT (80 characters or less)

Hearing Assessment in Neurofibromatosis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.	E. Elkins, Audiologist, CDP, NINCDS
Other:	A. Pikus, Audiologist, CC
	R. Eldridge, Chief Clinical Neurogenetics Studies, IRP, NINCDS

COOPERATING UNITS (if any)

Clinical Neurogenetics Branch, NINCDS
Cancer Epidemiology Branch, NCI

LAB/BRANCH

Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.20	.20	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An interdisciplinary clinic has been staffed for the evaluation of patients with neurofibromatosis and their families. Because the disorder has a dominant inheritance pattern, each child of a parent has a 50-50 chance of developing it. Of the two distinct forms of the disorder, the central form has a high incidence of bilateral acoustic neuromas. These benign tumors tend to develop on both the right and left auditory nerves causing both hearing and equilibrium problems. Evaluation of this patient population is being undertaken to provide recommendations for treatment and follow-up by the referring primary-care physicians.

Project Description:

Objectives: To develop reliable techniques for the assessment of hearing disorders associated with neurofibromatosis. We are cooperating with specialists in genetics and genetic counseling, neurology, neurosurgery, orthopedics, physical medicine and rehabilitation, otolaryngology, dermatology, radiology and cancer to develop recommendations for treatment of these patients and their families. Bilateral acoustic neuromas may be a hallmark of the central form of neurofibromatosis and are being documented in this study.

Methods Employed: In addition to routine procedures, evoked potentials to acoustic stimuli presented through earphones are being obtained. With an active electrode placed on the vertex of the head; a reference electrode on the earlobe receiving the stimuli; and a ground electrode on the contralateral earlobe, we record responses which occur within 10 msec after click stimulation. The intensity of the signals ranges from inaudible levels up to 125 dB sound pressure level (SPL). Levels of stimuli presentation are selected for the individual subject. At no time is the subject sedated.

Major Findings: No definitive findings are reportable at this time. Tentatively, we feel that abnormal amplitudes and latencies of Waves 1-3 are indicative of probable eighth nerve involvement.

Significance to NINCDS and Biomedical Research: This project relates to the National Research Strategy goal #65 which states: Research on the identification and quantification of auditory function, in order that patients with hearing disorders and diseases may be properly evaluated and effectively treated.

Proposed Course of Project: In addition to evaluating all patients presented by the interdisciplinary - study group, we are developing normative data with our instrumentation for average normal hearing (18-25 years); young adults (26-50 years); older adults (50-70 years); young children (2-8 years); and the group between 9 and 17 years of age.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02441-01 CDP

PERIOD COVERED

April 1, 1980 - September 30, 1980

TITLE OF PROJECT (80 characters or less)

Hearing Assessment in Neurofibromatosis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. E. Elkins, Audiologist, CDP, NINCDS
Other: A. Pikus, Audiologist, CC
R. Eldridge, Chief Clinical Neurogenetics Studies, IRP, NINCDS

COOPERATING UNITS (if any)

Clinical Neurogenetics Branch, NINCDS
Cancer Epidemiology Branch, NCI

LAB/BRANCH

Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
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Methods Employed: In addition to routine procedures, evoked potentials to acoustic stimuli presented through earphones are being obtained. With an active electrode placed on the vertex of the head; a reference electrode on the earlobe receiving the stimuli; and a ground electrode on the contralateral earlobe, we record responses which occur within 10 msec after click stimulation. The intensity of the signals ranges from inaudible levels up to 125 dB sound pressure level (SPL). Levels of stimuli presentation are selected for the individual subject. At no time is the subject sedated.

Major Findings: No definitive findings are reportable at this time. Tentatively, we feel that abnormal amplitudes and latencies of Waves 1-3 are indicative of probable eighth nerve involvement.

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ANNUAL REPORT

October 1, 1979 through September 30, 1980

Fundamental Neurosciences Program

National Institute of Neurological and Communicative Disorders and Stroke

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ANNUAL REPORT
October 1, 1979 - September 30, 1980
Fundamental Neurosciences Program
National Institute of Neurological and
Communicative Disorders and Stroke

The Fundamental Neurosciences Program (FNP) supports research in neuroanatomy, neurophysiology, neurochemistry and neuropsychology--the basic disciplines which underpin the clinical investigation of neurological diseases. These studies enlarge both the intrinsic knowledge of the nervous system and the methodology by which clinical problems may be approached. The FNP encompasses a large range of subject matter from artificial membranes to the neurobiological basis of learning in simple nervous systems. It is divided into three subprograms: General Fundamental Neurosciences, Neural Prosthesis, and Biomedical Engineering.

FNP receives approximately one-fourth of the grant applications received by NINCDS. They tend to be of relatively high quality in that approximately 90% are recommended for approval by initial review groups. During FY 1980, approximately 50% of those approved were funded. The portfolio currently contains 427 regular grants and 10 program projects supported at a level of approximately 30 million dollars. Responsibility for the support of neuroendocrinology was transferred to the Neurological Disorders Program during FY 1980. This rapidly expanding field of neuroscience had developed to the stage of clinical application in a variety of different directions (control of pain through enkephalins and endorphins, reversal of memory deficits with vasopressin, the role of hypothalamo-pituitary-adrenal axis in depression).

The Neural Prosthesis Program, directed by Dr. F.T. Hambrecht, is an important facet of FNP activity. The ultimate objective is to compensate for lost sensory or motor capacities through the chronic implantation of various devices (control of limb movement and bladder evacuation in quadriplegics, stimulation of the auditory nerve in the deaf). Under primary study is the area of interface between electrodes and tissue where numerous difficult problems remain to be solved. Tissue damage must be minimized, optimal parameters of current flow established, electrode toxicity eliminated, and failure of electrical components prevented. This program is primarily supported through research contracts at a level of about 2.2 million dollars a year.

GENERAL FUNDAMENTAL NEUROSCIENCES

Most of the regular research grants in FNP are in the field of neurochemistry (42%) or neurophysiology (41%). About 12% of the grants are for neuroanatomical studies. Other biological sciences, psychobiological relationships, neural prostheses, and biomedical engineering account for a few percent each.

Two program projects are involved with neuroanatomical studies, four with neurophysiological studies, three with neurochemistry, and one with biomedical engineering.

The Enteric Nervous System

Until relatively recently, research in this area has languished, possibly because the enteric nervous system was considered a simple relay in the parasympathetic innervation of the gut. However, at one time it was considered a separate division of the autonomic nervous system because of the discrepancies between the small number of fibers in the vagus nerves, as these pass through the diaphragm, and the large number of ganglion cells in the gut. It was also recognized early that the isolated gut could manifest pressure-induced reflex activity associated with the peristaltic reflex. This implied that the enteric nervous system contains sensory receptors, primary afferent neurons, integrative neurons and motor neurons--components of a primitive integrated nervous system.

Chemically also, the system is proving complex. Well-established neurotransmitters include acetylcholine, norepinephrine and serotonin. There is also evidence for the activities of dopamine, GABA, ATP, substance P, vasoactive intestinal peptide, leu-enkephalin, somatostatin and neurotensin.

The function of each of the various neurons is not certain. Cholinergic neurons are excitatory to intestinal smooth muscle, but also inhibit release of norepinephrine from adrenergic nerves. Adrenergic nerves inhibit intestinal motility either by hyperpolarizing smooth muscle directly, or by presynaptically inhibiting the release of acetylcholine. The smooth muscle also receives a nonadrenergic, non-cholinergic inhibitory innervation by a "purinergic" neuron releasing ATP at its terminal.

The enteric nervous system, because of its limited behavioral repertoire, accessibility, and capacity to function well *in vitro* should prove an excellent model with which to integrate structure, funtion and chemistry.

Neuroimmunomodulation

The effect of the central nervous system on general immunological reactions of the body is an area of growing interest. At the International Congress of Physiological Sciences in Budapest, a half-day session was devoted to this topic, and a volume summarizing current research trends in this area (edited by an NINCDS grantee) will shortly be published.

There is no question that immunological responses may be altered by hypothalamic lesions, "stress", and adrenocortical steriods. It remains to be determined whether most of the changes observed result from fluctuations in adrenocortical activity. Recent studies have centered upon the thymus gland, an organ partly lymphoid and partly endocrine in function. It produces the T-lymphocytes and a large number of peptides whose functions are not well understood. However, at least some of these substances are required for

T-cell and B-cell maturation. The innervation of the thymus has been clarified somewhat by new research into the problem. It appears that the thymus receives sympathetic fibers from adjacent ganglia and parasympathetic fibers from the nucleus ambiguus. After denervation it remains functionally active at about half its normal level. Obviously, much remains to be done to define the potential modulatory influence of the nervous system.

Neuroanatomical Asymmetry in the Human Temporal Lobes

The investigation of neuroanatomical asymmetry in the human temporal lobes and related psychological characteristics is continuing with contract support at McMaster University. Currently, approximately 60 terminal cancer patients have undergone some testing and 26 brains have been obtained for anatomical analysis. The results should provide a clue to the nature of hemispheric specialization. It is especially noteworthy that protocols were devised to permit measurements to be correlated with postmortem neuroanatomy. Much important information on the human brain could be obtained utilizing similar procedures.

Neurophysiology of Cognitive Processes

In July a Program Announcement was issued expressing interest in research grant applications in the field of the neurophysiology of cognitive processes. Initial response from investigators indicates a high level of interest in such studies. It is expected that the first applications will be received by November 1, 1980.

Local Neuronal Interactions

As a result of our Program Announcement of June 30, 1978, the FNP received 48 applications during FY 1980. More than 90% of them were recommended for approval, and of these over 50% were funded. The research proposed included work on both invertebrates and vertebrates and the approaches included neurochemistry, neuroanatomy, neurophysiology and mathematics. Among the areas of the nervous system studied were the retina, hippocampus, hypothalamus and autonomic ganglia. The first experimental results should be available within a year.

Scientific Information Exchange

FNP has supported two information exchange activities, the Brain Information Service (BIS) at UCLA (under contract) and the Neurosciences Research Program (NRP) at M.I.T. (under grant).

BIS has made available alerting bulletins, recurrent bibliographies, and reference bibliographies covering areas of interest to basic neuroscientists. The BIS contract terminated January 14, 1980. With the cooperation of the National Library of Medicine (NLM), a set of neuroscience search strategies has been prepared (computer index terms with instructions). These strategies are designed to help scientists obtain monthly printouts of references in the NLM data base on (1) Sleep (2) Neuroendocrine Control Mechanisms (3) Neurochemical Transmitters (4) Developmental Neurobiology (5) Cerebral Evoked

Potentials (6) Neuroimmunology and (7) Peptides of the nervous system. The search strategies can be used "as is" or can be custom tailored to the scientist's research interest. Initial response from investigators has been favorable.

The Neurosciences Research Program (NRP) is an off-campus Branch of the Massachusetts Institute of Technology located at Jamaica Plains, Massachusetts. Founded in 1962 with the main objective of bringing scientists engaged in basic studies in the nervous system together with others from different disciplines, such as chemistry, physics and mathematics, it was anticipated that the interaction between investigators with widely differing scientific backgrounds would lead to rapid exchange of new concepts and developing technologies in a manner that would accelerate the understanding of nervous systems. Approximately eight sessions per year have been convened on topics selected when the time was right for a review of current knowledge and an assessment of areas that were obscure and poorly understood. From these meetings new conceptual approaches to issues have emerged and information has been made available rapidly to the scientific community. The NRP continues to be a valuable resource for the FNP often indicating present and future valuable lines of research. The publications serve the entire neuroscience community.

NEURAL PROSTHESIS

Recent findings from neural prosthesis research projects supported by contracts are briefly described in the attached narratives. A major result has been the development and fabrication of tantalum capacitor electrodes which are small enough for intracortical implantation. Prototypes of these electrodes are presently being evaluated in monkey motor cortex by members of the NINCDS Laboratory of Neural Control. A significant problem that remains unsolved is breakage of ultraminiature, flexible leads that connect electrode arrays to implanted neural stimulators. This problem is preventing the clinical evaluation of a neurogenic bladder evacuation system. Several possible solutions are presently being evaluated.

A byproduct of the auditory prosthesis research is a new theory of auditory signal processing by the brain. The electrode arrays being fabricated under contract will permit the experimental evaluation of this theory as well as testing of multichannel auditory prostheses in deaf individuals.

BIOMEDICAL ENGINEERING

The Biomedical Engineering Program consists of one contract for the development of transdermal stimulators (for auditory prostheses, cerebellar stimulation in studies of movement disorders, and for bladder evacuation), and one program project grant that focuses on the design and development of state-of-the-art instrumentation for both basic and clinical neuroscience research.

The program emphasis will continue to concentrate on responding to the needs of basic and clinical researchers by supporting the design and development of devices and instrumentation which are not commercially available or which could not be produced commercially without a significant amount of research and development. The staff of the Biomedical Engineering Program will also continue to assist other NINCDS programs in designing, developing and evaluating bioengineering aspects of their research projects.

APPENDIX

PROGRAM ANNOUNCEMENT

The FNP issued the following Program Announcement in the July 18, 1980 issue of the NIH Guide for Grants and Contracts

The Neurophysiology of Cognitive Processes

The Fundamental Neurosciences Program (FNP) of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) encourages the submission of applications for research grants in the neurophysiology of cognitive processes.

PURPOSE AND SCOPE

This announcement is intended to stimulate new approaches to the experimental and conceptual aspects of research on those types of cognitive processes which can be studied at the neural level in both animal and human research. A primary goal should be to characterize the sources and time course of neural activity (where feasible in its relation to unit activity) related to these processes.

Projects of the following types illustrate this area:

1. Animal research
   - a) Involving innovative methods and concepts for the definition and analysis of cognitive processes in experiments that are designed in response to new knowledge about the nervous system.
   - b) Applying recently established knowledge about cognitive processes in humans to the design of neurophysiological experiments in animals.
   - c) Requiring collaboration between scientists who are expert in the cognitive sciences and those who are expert in the neurobiological sciences.
2. Human research
   - a) Developing new methods, concepts, and paradigms for research on cognitive processes that lead specifically toward studies of the underlying neural activites.
   - b) Applying recent advances in neurobiology to experiments using clinical neurophysiological and/or neuropsychological approaches to the study of cognitive processes.
   - c) Bringing experts in neurobiological research into collaboration with cognitive scientists.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1979 - January 14, 1980

Contractor: University of California at Los Angeles, Brain Information Service (UCLA-BIS) (N01 NS 9-2304)

Title: Operation of Specialized Information Center in Brain and Other Neurosciences

Contractor's Project Director: Michael H. Chase, Ph.D.

Current Annual Level of Support: $330,000

Objectives: The contractor operates a specialized information center, which serves as a national focal point for the identification, collection, storage, retrieval, analysis, repackaging, and dissemination of information on non-clinical neurosciences. The major thrusts of this information center are information analysis products and services using the identified and stored information. The contractor makes available comprehensive information services, including: current alerting bulletins, recurrent bibliographies, and reference bibliographies.

Major Accomplishments: During the current contract period, the Brain Information Service carried out the following activities:

Current Alerting Bulletins

Neurochemical Transmitters and Modulators (Twice Monthly)
Sleep Bulletin including Sleep Review (Monthly)
Memo of Current Books in the Brain Sciences (Incl Author Index)(Monthly)
Developmental Neurobiology (Monthly)

Recurrent Bibliographies (Six Issues/Year)

Neuroimmunology
Cerebral Evoked Potentials
Endorphins

Bibliographic Cumulations

Sleep Research - Volume 8

Significance to Biomedical Research and the Program of the Institute: The Brain Information Service has served the biomedical community by the maintenance of a very extensive data base devoted to the fundamental neuroscience literature. In addition, a number of synthetic and analytic information products are produced by the staff for distribution to the neuroscience community.

Proposed Course of Contract: This contract expired on January 14, 1980. The Brain Information Service is currently being supported under a contract from the Office of the Director, NIH.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1979 through September 30, 1980

Contractor: UNIVERSITY OF ROCHESTER (N01-NS-0-2279)

Title: Development of a Sensory Prosthesis

Contractor's Project Director: Robert Doty, M.D.

Current Annual Level of Support: $0

Objectives: The stability of the threshold of excitation of nerve cells in the visual cortex during long-term electrical stimulation was studied in monkeys. Some of the mechanisms causing increases in threshold for detection of stimulation and some means for preventing these increases were evaluated.

Major Findings: There were no major findings in this period because the investigators were on a no-cost extension to prepare their final report.

Significance to Biomedical Research and to the Program of the Institute: This work will be useful for developing safe and efficient methods of stimulating the central nervous system for use in neural prostheses for the neurologically handicapped.

Proposed Course of Contract: This contract will terminate in September 1980.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1979 through September 30, 1980

Contractor: UNIVERSITY OF CALIFORNIA, SAN FRANCISCO (N01-NS-3-2307)

Title: Studies of Urinary Bladder Evacuation by Electrical Stimulation

Contractor's Project Director: Emil Tanagho, M.D.

Current Annual Level of Support: $105,446

Objectives: Studies are being conducted in animals with upper motor neuron lesions to determine the feasibility of urinary bladder evacuation by electrical stimulation of the sacral spinal roots. Studies are also being carried out on methods of preventing urinary incontinence.

Major Findings: 1. Electrodes implanted on the sacral roots of spinal dogs undergo significant movement with respect to the bony vertebral column while the animal moves about his cage. This movement has placed tension on the electrode connecting leads and on the electrode cuff around the sacral nerve causing damage to the nerve. 2. The spiral electrode developed by Huntington has proved to be the most flexible and the least traumatic of the electrode types evaluated to date. However, in one of three animals implanted with this electrode, pain is evident indicating current spread from the spiral electrode.

Significance to Biomedical Research and to the Program of the Institute: The restoration of the ability of persons with neurogenic bladders to empty their bladders voluntarily is a long-range goal of this work and would reduce urinary tract infections that are a major cause of death in paraplegics and quadriplegics. The problem of urinary incontinence is of both social and medical significance, especially in the geriatric population.

Proposed Course of Contract: When a reliable electrode and lead system has been demonstrated by successful tests of at least five months implantation in at least five spinal dogs, the bladder evacuation system will be implanted in humans with neurogenic bladders. Following implantation, an extensive evaluation of the effects of stimulation on the bladder pressure, the urine flow rate, and the residual urine remaining in the bladder will be conducted to determine the effectiveness of the prosthesis.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1979 through September 30, 1980

Contractor: UNIVERSITY OF CALIFORNIA, LOS ANGELES (N01-NS-4-2331)

Title: Studies on the Effects of Electrical Stimulation of the Cerebellum

Contractor's Project Director: Thomas Babb, Ph.D.

Current Annual Level of Support: $0

Objectives: The effects of cerebellar stimulation on hippocampal neurons are being studied, and brain stem projections to the hippocampus are being elucidated.

Major Findings: 1. Using single unit extracellular and intracellular recording techniques with electrodes in subicular principal neurons, the presence of a substantial, caudally directed excitatory projection from hippocampal pyramidal neurons onto subicular neurons was demonstrated. 2. Excitatory synapses are located on the dendrites of subicular pyramidal cells and inhibitory synapses are located somatically.

Significance to Biomedical Research and to the Program of the Institute: These studies should provide information on the mechanisms, if any, by which cerebellar stimulation modifies clinical seizures and movement disorders. Studies of midbrain and brain stem inhibitory projections to the hippocampus may provide pathways for control of temporal lobe seizures.

Proposed Course of Contract: This contract is completing its final year and will be terminated in December 1980.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1979 through September 30, 1980

Contractor: UNIVERSITY OF MINNESOTA (N01-NS-4-2332)

Title: Study of the Effects of Electrical Stimulation of the Cerebellum

Contractor's Project Director: Dr. James Bloedel

Current Annual Level of Support: $97,143

Objectives: The effects of cerebellar stimulation on primate models of spasticity and movement disorders are being evaluated. The neurophysiological mechanisms and anatomical pathways associated with such stimulation are being examined.

Major Findings: 1. In all experiments performed, the neurophysiological effects of cerebellar stimulation have been immediate. This contrasts with clinical claims by others of effects delayed by hours and days. 2. Stimulus frequency dependent effects of cerebellar stimulation on stretch reflexes have been documented. A marked reduction in the amplitude of the gastrocnemius-soleus stretch reflex was noted at stimulation frequencies above 200 hz but not at lower frequencies. 3. Further quantification of the inhibition of monosynaptic reflexes by cerebellar stimulation has been achieved.

Significance to Biomedical Research and to the Program of the Institute: These studies should provide information on the neurophysiological mechanisms, if any, by which cerebellar stimulation modifies normal movement and movement disorders.

Proposed Course of Contract: This contract terminates at the end of September 1980. Competitive requests for proposals for continuation of this work have been released.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1979 through September 30, 1980

Contractor: STANFORD UNIVERSITY (N01-NS-5-2306)

Title: Transdermal Stimulation Electronics for Auditory Prostheses

Contractor's Project Director: Robert White, Ph.D.

Current Annual Level of Support: $147,739

Objectives: Design, development, and fabrication of transdermal stimulators to be used in the evaluation of multichannel cochlear implant auditory prostheses.

Major Findings: 1. A redesign of the titanium hermetic package has required reducing the number of channels from 12 to 8 because of space limitations. Prototypes of the latter system have been fabricated, and *in vitro* testing has begun. 2. The design of the next generation system with regulated current output and a more flexible pulse timing scheme has begun.
3. Preliminary calculations of radio-frequency coil dependence on separation, axis alignment, and axis tilt were completed.

Significance to Biomedical Research and to the Program of the Institute:
The Institute is presently supporting, under the grant mechanism, the evaluation of multichannel auditory prostheses. This contract will provide electronic stimulators to several of these grantees.

Proposed Course of Contract: About 25 new transdermal stimulation systems with regulated current outputs are needed for *in vitro* and *in vivo* testing. Development and fabrication of these units will take place in the next year. The design requirements of transdermal stimulators are continuously being revised by physiologists on the basis of new data from ongoing cochlear implant studies.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1979 - September 30, 1980

Contractor: McMASTER UNIVERSITY (NO1-NS-6-2344)

Title: Neuroanatomical Asymmetry in the Human Temporal Lobes and Related Psychological Characteristics

Contractor's Project Director: Sandra F. Witelson, Ph.D.

Current Annual Level of Support: $51,000

Objectives: Patients in good neurological and mental health at a cancer clinic are approached by a trained "clinical coordinator" about granting permission for autopsy and taking psychological tests. The tests are those demonstrated to be affected by cerebral lesions of the temporal lobe on the left or right; certain variations in anatomical asymmetry in the two normal temporal lobes will be investigated for relationships to the test scores.

Major Findings: As of June, 59 patients signed consent forms, and 56 have undergone some testing. Some brains are not obtained; 26 specimens have become available. New histological procedures have been developed with Dr. Marc Colonnier, for the analysis of selected brains. Of the six brains with some preliminary gross measures, one has shown an interesting confirmation of a theory for reversed asymmetry.

Significance to Biomedical Research and to the Program of the Institute: The research bids well to help solve some basic questions of why nearly a quarter of human brains do not show the temporal lobe asymmetry of the two-thirds majority; the results should provide some insight into the nature of the hemispheric specialization of the human brain.

Proposed Course of Contract: Testing of patients is expected to continue for another year before the funding expires (one extension was granted, and another will be applied for--their expenses have been less than were originally expected, in part as a result of the devaluation of the Canadian dollar). The histological analysis of eight extreme brains (four left and four right temporal lobe areas larger) should be completed in the next year.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1979 through September 30, 1980

Contractor: STANFORD UNIVERSITY (N01-NS-7-2366)

Title: Development of Multichannel Stimulating Electrodes

Contractor's Project Director: Robert White, Ph.D.

Current Annual Level of Support: $169,273

Objectives: State-of-the-art microelectronic techniques are being applied to the design and development of second generation multielectrode arrays for stimulation of the eighth nerve in the human modiolus. These electrodes will be used for the evaluation of the feasibility of a multichannel auditory prosthesis.

Major Findings: 1. In the fabrication of rigid tantalum-on-sapphire modiolar electrode arrays, adhesion of platinum (sputtered onto the tantalum) at the stimulation sites can be achieved by annealing the electrode array. This leads to interdiffusion and alloying of the two metals. 2. The thickness of platinum following sputtering can be increased by electroplating platinum onto the sputtered platinum. 3. The problem of obtaining adhesion of platinum to polyimide in the flexible thin film scala tympani electrodes has not been solved. Attempts to use tantalum as an intermediate metal did not improve adhesion.

Significance to Biomedical Research and to the Program of the Institute: Multichannel electrode arrays for stimulation of the eighth nerve may provide a means of communication for sensory deaf individuals. The NINCDS is committed to determining the feasibility of auditory prostheses for the deaf.

Proposed Course of Contract: This contract expires in August 1980. A competitive request for proposals was issued to continue this work and Stanford University was one of the successful offerors.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1979 through September 30, 1980

Contractor: UNIVERSITY OF CALIFORNIA, SAN FRANCISCO (N01-NS-7-2367)

Title: Development of Multichannel Stimulating Electrodes

Contractor's Project Director: Michael Merzenich, Ph.D.

Current Annual Level of Support: $157,518

Objectives: The electrical and mechanical properties of the scala tympani are being studied and on the basis of these results, multichannel stimulation electrode arrays are being developed which are suitable for stimulation of the eighth nerve in humans.

Major Findings: 1. A new design of multichannel scala tympani electrode arrays has been completed. This design includes electrodes with larger surface areas, new electrode fabrication dies, and a new method of guiding the electrode wires through the array in a "central rib" configuration. 2. Measurements on human cadaver cochleas have revealed that the height of the scala tympani is not a continuously decreasing function from the round window to the apex but that in most temporal bones the height is actually greater at the 20 to 22 mm position than it is 8 to 10 mm basal to that region. 3. In the region from about 12 to 20 mm from the round window, the height of the scala tympani in different individual cochleas may vary as much as 500 to 600 microns.

Significance to Biomedical Research and to the Program of the Institute: Multichannel electrode arrays for stimulation of the eighth nerve in the scala tympani may provide a means of communication for sensory deaf individuals. This Institute is committed to determining the feasibility of auditory prostheses for the deaf.

Proposed Course of Contract: This contract will lead to the development of multichannel electrodes suitable for implantation in the scala tympani of humans as part of an auditory prosthesis for the deaf. A competitive request for proposals was released in the early part of 1980, and this contractor was one of the successful offerors. The present contract will terminate in August 1980, and the new contract will begin in September 1980.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1979 through September 30, 1980

Contractor: GINER, INC. (N01-NS-8-2300)

Title: Development of Improved Capacitor Stimulating Electrodes

Contractor's Project Director: Harry Lerner, Ph.D.

Current Annual Level of Support: $139,000

Objectives: Research on methods of increasing the charge storage capability per unit volume and the current density output capability of capacitor electrodes that are suitable for stimulation of neural tissue is being carried out.

Major Findings: 1. Tantalum electrodes based on sintering a slurry of tantalum powder and glycerin have been reproducibly fabricated. 2. Twenty of these electrodes with a diameter of 200 microns were supplied to the Project Officer for evaluation at NIH in monkey motor cortex. Initial results indicate that these electrodes are stable and that their charge storage capability is well above that required for exciting neurons with electrodes of this size. Single unit neural activity has also been recorded from these electrodes.

Significance to Biomedical Research and to the Program of the Institute: The capacitor stimulating electrode is the safest method presently available to stimulate neural tissue. Improvement in its stimulating capabilities and methods of reducing its physical size will permit the development of more sophisticated and safer neural prostheses which utilize stimulation of central nervous system tissue.

Proposed Course of Contract: The smallest capacitor electrode that has been fabricated to date has been 200 microns in diameter. In order to produce usable electrodes with smaller diameters, the charge storage capability of the electrodes must be increased. This will be the contractor's major concern during the next year.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1979 through September 30, 1980

Contractor: EIC CORPORATION (N01-NS-8-2392)

Title: Development of Improved Capacitor Stimulating Electrodes

Contractor's Project Director: Barry Brummer, Ph.D.

Current Annual Level of Support: $121,000

Objectives: Improvements in the charge storage capability per unit volume and the current density output capability of capacitor electrodes suitable for intracortical stimulation of neural tissue are the major objectives. Prototype capacitor electrodes will be fabricated and supplied to other investigators.

Major Findings: 1. Using an etching technique to increase the real surface area of tantalum capacitor electrodes, reproducible electrodes with maximum charge storage capabilities of 34.5 microcoulombs/mm^3 have been achieved. 2. Attempts to mask tantalum wire specimens during electrophoretic powder deposition by applying anodic oxide films to the shaft have failed because of the embrittlement of the tantalum by the oxygen during the sintering process. 3. Electrodes fabricated using the electrophoretic process have surface areas increases 22 times the geometric area and capacitances up to .24 microfarads per geometric mm^2.

Significance to Biomedical Research and to the Program of the Institute: The capacitor stimulating electrode is the safest method presently available to stimulate neural tissue. Improvement in its stimulating capabilities and methods of reducing its physical size will permit the development of more sophisticated and safer neural prostheses which utilize stimulation of neural tissue.

Proposed Course of Contract: The contractor is beginning an exploration of barium titinate as a dielectric in capacitor electrodes. Attempts to increase the charge storage capability of tantalum capacitor electrodes will also be continued.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1979 through September 30, 1980

Contractor: UNIVERSITY OF MISSOURI (N01-NS-8-2393)

Title: Biomaterials for Neural Prostheses

Contractor's Project Director: Allen Hahn, Ph.D.

Current Annual Level of Support: $207,000

Objectives: Development of new biomaterials for use as implant encapsulants, primers, and lead insulators.

Major Findings: 1. Glow discharge polymerized methane (GDP-methane) adheres to platinum with a strength of adhesion, an order of magnitude greater than that of Parylene to platinum. 2. GDP-methane appears to be electrically anisotropic.

Significance to Biomedical Research and to the Program of the Institute: Many implanted devices that are presently available or are planned for the future are adversely affected by water and sodium ions in extracellular fluid. Development of improved encapsulation and sealing systems to prevent their access to the implants will be useful not only to neural prostheses, but to other artificial organs that involve implanted electronics.

Proposed Course of Contract: The contractor has just completed construction of a facility for laying down plasma polymerized polymers in the same chamber that Parylene is deposited. This will permit the evaluation of plasma polymers as "primers" between known, biologically compatible, biomaterials and the implant substrates. Also, plasma polymerized polymers will be developed as encapsulants and lead insulators.

CONTRACT NARRATIVES
Fundamental Neurosciences Program, NINCDS
October 1, 1979 through September 30, 1980

Contractor: CITY UNIVERSITY, LONDON (N01-NS-8-2394)

Title: Biomaterials for Neural Prostheses

Contractor's Project Director: Dr. William Wake

Current Annual Level of Support: $59,000

Objectives: Improvement of the adhesion of insulators to conductors and other insulators that are used as implant packages, encapsulants, sealants and lead insulators in implanted neural prostheses.

Major Findings: 1. The water transmissability of room temperature vulcanized silicone rubber was measured and compared with the water absorption. An average value of 30 $g/m^2/day/cmHg/cm$ thickness was found. This is about 10 times greater than varieties of silicone rubber which are not room temperature vulcanized. 2. Silicone rubber samples immersed in water absorb water but actually shrink due to leaching of material from the rubber. The change in weight of samples of known size as a function of time has been measured.

Significance to Biomedical Research and to the Program of the Institute: Many implanted devices that are presently available or are planned for the future are adversely affected by water and sodium ions in extracellular fluid. Development of improved sealing systems to prevent access of water and sodium ions to the implants will be useful not only to neural prostheses, but to all artificial organs that involve implanted electronics.

Proposed Course of Contract: This project is in its second year and will be extended to include a study of the silicone rubber-platinum interface as well as adhesion of various biomaterials to tantalum pentoxide.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1979 through September 30, 1980

Contractor: EIC CORPORATION (N01-NS-9-2315)

Title: Safe Procedures for Electrical Stimulation of the Nervous System

Contractor's Project Director: Barry Brummer, Ph.D.

Current Annual Level of Support: $106,695

Objectives: The electrochemical processes that occur at the electrode-electrolyte interface and methods of reducing undesirable reactions are being studied.

Major Findings: 1. A method of utilizing the voltage transient developed across the stimulating electrode during pulsing has been developed that supplies information about potentially toxic electrochemical reactions that are occurring. 2. The conditions under which proteins protect electrodes from corrosion have been further studied.

Significance to Biomedical Research and to the Program of the Institute: Development and evaluation of safe stimulating techniques for use in neural prostheses are major goals of the Neural Prosthesis Program of the Institute.

Proposed Course of Contract: This contract has been in effect for only nine months and will continue at least two more years.

CONTRACT NARRATIVE

Fundamental Neurosciences Program, NINCDS
October 1, 1979 through September 30, 1980

Contractor: ELECTROCHEMICAL TECHNOLOGY CORPORATION (N01-NS-9-2316)

Title Electrochemical Studies

Contractor's Project Director: Dr. Theodore Beck

Current Annual Level of Support: $102,730

Objectives: New stimulation electrodes based on ion selective membranes will be developed and fabricated.

Major Findings: 1. Seven types of Actrodes have been designed. These differ in the physical shape and configuration of the ion exchange membrane. All consist of a silver ball coated with silver-silver chloride which in turn is coated with the ion exchange membrane. 2. Adhesion of the ion exchange membrane to the silver-silver chloride has been a significant problem. 3. The resistivity of silver-silver chloride has ranged from 30 kilohms cm to 100 kilohms cm for electrodes fabricated with a 10,000 angstrom silver-silver chloride layer. 4. Both Chitosan and Melamine are undergoing evaluation as ion exchange membrane.

Significance to Biomedical Research and to the Program of the Institute: Neural prostheses that utilize functional electrical stimulation require safe techniques for long-term neuronal activation and inhibition. This work will provide a better understanding of the electrochemical factors involved and develop new electrodes based on these findings.

Proposed Course of Contract: This contract began in January 1980 and will continue for at least two more years.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1979 through September 30, 1980

Contractor: HUNTINGTON INSTITUTE OF APPLIED MEDICAL RESEARCH (N01-NS-0-2319)

Title: Safe Methods of Electrical Stimulation

Contractor's Project Director: William Agnew, Ph.D.

Current Annual Level of Support: $224,904

Objectives: The histopathological effects of long-term electrical stimulation of the nervous system in animals are being studied with various electrode designs, stimulus wave forms, and stimulus parameters. Major emphasis is on intracortical electrodes and peripheral nerve stimulating electrodes. During stimulation, ion-sensitive electrodes are used to monitor changes in extracellular ion concentrations. When long-term stimulation is completed, the tissues surrounding the electrodes are examined using both light and electron microscopy.

Major Findings: 1. Studies of sacral nerve roots which have been stimulated through nerve cuff electrodes for periods from two to six months have shown significant atrophy of the fibers and apparent extrusion of the nerve trunks from the electrode cuffs. It now appears that tension on the cuff exerted by the connecting leads to the stimulator was responsible for the separation of the nerve trunk from the cuff. 2. A new type of spiral electrode cuff has been designed which reduces trauma to the sacral roots. 3. Ion-sensitive microelectrodes for the detection of potassium and calcium ion concentrations in the cerebral extracellular space have been successfully fabricated and tested *in vivo*. 4. During stimulation, extracelluar potassium rises abruptly to a value determined by the stimulus level. The potassium concentration then falls somewhat and maintains a level between the resting state and the peak state until stimulation terminates. 5. Under similar conditions, extracellular calcium shows a slow but continuous decrease. The time course of this decrease is much slower than the increase in extracellular potassium.

Significance to Biomedical Research and to the Program of the Institute: These studies are important for determining the safety and efficacy of various forms of neural stimulation utilized in neural prostheses for the neurologically handicapped.

Proposed Course of Contract: This contract began in January 1980 and will extend for at least two more years.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1979 through September 30, 1980

Contractor: CASE WESTERN RESERVE UNIVERSITY (N01-NS-0-2330)

Title: Study of Intramuscular Electrical Stimulation of Muscle

Contractor's Project Director: Thomas Mortimer, Ph.D.

Current Annual Level of Support: $278,836

Objectives: The use of electrical stimulation of the neuromuscular system in animals and humans for artificial control of muscle and generation of purposeful movements is being studied. The ultimate goal is to restore function to the upper extremities in patients paralyzed as the result of spinal cord injuries.

Major Findings: 1. A new source of command signals for control of muscle stimulators in paralyzed individuals has been derived from the sternocleidomastoid muscle. Its advantages are ease of mounting of surface electrodes, relative insensitivity of the command level with different electrode positions, and rare inadvertent command signal generation. 2. Studies on the control of elbow position were initiated with electrodes in the lateral head of the triceps. When two electrodes in the triceps are stimulated simultaneously, the force generated results in nearly full elbow extension in all positions of shoulder abduction. 3. A transducer has been developed that detects deviations of the gravity vector from vertical. This transducer will be interfaced with the elbow stimulation system to automatically provide tricep stimulation when the elbow is elevated above the horizontal plane. 4. Multistrand stainless steel electrodes continue to show longer lifetimes and are more reliable than single strand stainless steel electrodes.

Significance to Biomedical Research and to the Program of the Institute: The techniques being investigated are restoring lost function to paralyzed individuals.

Proposed Course of Contract: This contract began in June of this year and will continue for at least two more years.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1979 through September 30, 1980

Contractor: UNIVERSITY OF UTAH RESEARCH INSTITUTE (N01 NS 0-2335)

Title: Transducer Development and Evaluation of Sensory Feedback

Contractor's Project Director: Andrew A. Schoenberg, Ph.D.

Current Annual Level of Support: This contract was being negotiated during July 1980.

Objectives: The possibility of providing artificial pressure, force, slip and position information to quadriplegic patients has not been explored because of a lack of suitable transducers. This research will develop such transducer systems and evaluate them in a simulated model of a paralyzed hand controlled by functional neuromuscular stimulation.

Major Findings: Not applicable.

Significance to Biomedical Research and to the Program of the Institute: This research is part of a multidisciplinary approach to restoration of lost function in paralyzed individuals.

Proposed Course of Contract: This contract has not yet begun, and its proposed course is essentially the pursuit of the "objectives."

ANNUAL REPORT

October 1, 1979 through September 30, 1980

Neurological Disorders Program
National Institute of Neurological and Communicative Disorders and Stroke

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ANNUAL REPORT
October 1, 1979 - September 30, 1980

NEUROLOGICAL DISORDERS PROGRAM
NATIONAL INSTITUTE OF NEUROLOGICAL
AND COMMUNICATIVE DISORDERS AND STROKE
NATIONAL INSTITUTES OF HEALTH

ORGANIZATION OF REPORT

The Annual Report has four main sections. The first section is a brief administrative summary of the program, which is followed by a report from the Office of the Director, NDP with eight subsections. Although the Neurological Disorders of Early Life portfolio has been transferred to the Developmental Neurology Branch from the Office of the Director, this transfer was effected after the date of submission of the Annual Report. Therefore, the activities of this portfolio are described in the report of the OD, NDP. The third and fourth sections of the Annual Report are reports from the Developmental Neurology and Epilepsy Branches respectively.

PROGRAM SUMMARY STATEMENT

The Neurological Disorders Program (NDP) of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) consists of the Office of the Director, the Developmental Neurology Branch and the Epilepsy Branch. The Program has responsibility for the support of research directly or indirectly related to any of the medical neurological disorders except for stroke. The categories into which these disorders are grouped for administrative purposes are as follows:

Convulsive and Related Paroxsymal Disorders
  (administered within the Epilepsy Branch)
Demyelinating and Sclerosing Disorders
Disorders of Other Senses - Pain
Infectious Diseases of the Nervous System
Muscular and Neuromuscular Disorders
Neural Aspects of Learning and Behavior
Neuroendocrinological Studies
Neurological Disorders of Aging
Neurological Disorders of Early Life
  (administered within the Developmental Neurology Branch)

Organizational Changes in FY 1980

During FY 1980 the Epilepsy Branch assumed responsibility for administration of all of the research grant applications on convulsive disorders, including the Comprehensive Epilepsy Programs, and other paroxysmal disorders of the nervous system such as narcolepsy and cataplexy. This new activity is in addition to the past responsibilities of the Epilepsy Branch, which have been the administration of specialized Comprehensive Epilepsy Programs supported by contract, and an ongoing program to develop new anticonvulsive drugs, which is supported by direct operations, contracts and grants. During FY 1980, the Developmental Neurology Branch has assumed responsibility for the administration of a major portion of the grant portfolio previously classified as Disorders of Early Life. This activity is in addition to previously assigned responsibilities of completing the analysis and publication of data collected during the Institute's Collaborative Perinatal Project.

Changes in Personnel

During FY 1980, Dr. Roger Porter was appointed Chief of the Epilepsy Branch. Dr. Eugene Oliver joined the Office of the Director, NDP, to coordinate the activities of the Health Scientist Administrators and to expand activities in the Neurological Disorders of Aging. Drs. William Pitlick and Janet Trubatch joined the Office of the Director as Health Scientist Administrators to assume responsibility in the areas of epilepsy and convulsive disorders and in muscular and neuromuscular disorders, respectively.

Summary of Major Activities During FY 1980

Grant Activity

The major mechanism of the Program support is the investigator initiated research grant application. During FY 1980, the Program initiated four program announcements designed to encourage research in areas where it was felt that further effort was appropriate. One announcement was to encourage research in motor neuron or other neuron degenerative diseases. One was issued in the area of movement disorders and was intended to strengthen the research support in the neurological diseases associated with The aging process; another is presently being prepared on Alzheimer's Disease. A third announcement, in neuroendocrinology, was intended to stimulate research in the rapidly expanding area of neuroactive peptides which effect hormone receptors in the brain. The fourth program announcement on Reye's Syndrome, was intended to strengthen the Program's research effort in clinical pediatric neurology. The Program has made a deliberate effort to engage collaborative efforts with other Institutes. To accomplish this goal, the Program Announcement on Reye's Syndrome was issued in conjunction with the National Institute of Allergy and Infectious Diseases, the National Institute for Arthritis, Metabolism and Digestive Diseases, and the National Institute of Child Health and Human Development. It is planned to publish the announcement in Alzheimer's Disease jointly with the National Institute on Aging.

One major initiative begun in FY 1979, a Request for Applications for establishment of Huntington's Disease Centers Without Walls, was implemented with the award of two grants in FY 1980. The conversion of the support mechanism from contract to grant for the Program's Comprehensive Epilepsy Programs is underway. One grant was made in FY 1980; two remaining Comprehensive Epilepsy Programs have applications pending and will receive NANCDS Council action in FY 1981. The grant portfolio of the Disorders of Early Life, is being reevaluated with the intent of providing more emphasis on clinical pediatric neurological research. To achieve this goal, the Program will follow the announcement on Reye's Syndrome, with a program announcement requesting applications on Neonatal Brain Disorders. Other initiatives will follow in FY 1981.

Contract Activity

The bulk of the Program's contract funds are used by the Epilepsy Branch to support their continuing program to develop nore effective anti-epileptic drugs. Several promising compounds are moving through the Epilepsy Branch's Chronic Toxicity Screening Program. A Request for Proposals (RFP) for an initial clinical trial of anti-convulsive agents for intractable complex partial seizures, the most common cause of presently untreatable seizures in adults, will be issued in late FY 1980 for initial implementation in FY 1981. In addition, the Epilepsy Branch has awarded the final contract for support of a Comprehensive Epilepsy Center; directed toward the special problem of diagnosis, treatment and public education regarding epilepsy in urban areas with a significant minority population.

The analysis and publication of the National Collaborative Perinatal Project (NCPP) data by the Developmental Neurology Branch continues with the publication of monographs and articles in FY 1980. Microfilming of the original NCPP data records continues with final completion scheduled for mid FY 1981. The transfer of the original records to archival storage has begun. An RFP has been issued to establish a data management system for the NCPP records outside of the Institute so that interested members of the general biomedical public may have free access to the original data.

Direct Operation Activities in FY 1980

1) Program Advisory Committee

The Neurological Disorders Program organized an Ad Hoc Advisory Committee of outside experts to provide it with guidance for its activities. The Committee members are:

Floyd E. Bloom, M.D.	The Salk Institute
Robert G. Grossman, M.D.	Baylor College of Medicine
Robert J. Gumnit, M.D.	St. Paul-Ramsey Medical Center
Richard T. Johnson, M.D.	The Johns Hopkins University
Seymour Levine, M.D.	New York Medical College
Joseph B. Martin, M.D., Ph.D.	Massachusetts General Hospital
Dominick P. Purpura, M.D.	Albert Einstein College
J. Murdoch Ritchie, Ph.D., F.R.S.	Yale University
Joseph J. Volpe, M.D.	St. Louis Children's Hospital

Two meetings were held in FY 1980.

In FY 1980, the Neurological Disorders Program initiated a series of workshops with voluntary health agencies whose interests are in the area of responsibility of the Neurological Disorders Program. Three workshops were held in this fiscal year with three more scheduled for the next fiscal year to complete the cycle of inviting some 60-70 voluntary health agencies to Bethesda. Efforts are made to group voluntaries with similar interests at each of the workshops. These workshops have been particularly valuable in two areas: (1) the Program becomes informed of the activities of the voluntaries, particularly the research activities which they support; (2) the voluntaries become familiar with the procedures by which NINCDS provides research support, and the general areas of research support and types of award mechanisms available.

2) NDP Sponsored Workshops and Conferences

In addition to several workshops and conferences for which the Neurological Disorders Program provided financial support. The Program also provided substantial staff input into organizing, conducting, or manuscript editing for five workshops or conferences during FY 1980. These were:

(1) Neurosecretion and Brain Peptides: Implications for Brain Function and Neurological Disease.
(2) Consensus Development Conference on Febrile Seizures.
(3) Genetics and Epilepsy.
(4) XVIII International Symposium on Neurosecretion.
(5) Cellular Aggregation and Other Membrane Phenomena in Multiple Sclerosis: Mechanisms of Proposed Diagnostic Tests.

3) Information Services

Because of the limitation of contract funds, the Neurological Disorders Program has reevaluated its program information services and discontinued one contract, the Clinical Neurology Information Center, because it was felt that this information service could, in part, be covered by existing Institute services. In addition, the Program has decided to support some information transfer activities associated with the Comprehensive Epilepsy Programs by the grant, rather than contract, mechanism.

CONTRACT NARRATIVE
Neurological Disorders Program
October 1, 1979 - September 30, 1980

UNIVERSITY OF NEBRASKA (NO1-NS-2-2300)

Title: The Establishment and Operation of a Clinical Neurology Information Center

Contractor's Project Director: Walter J. Friedlander, M.D.

Current Annual Level of Funding: $133,000

Objectives: Operation of a specialized Information Center on Clinical Neurology. This Center will be an international focal point for information relating to those diseases of interest to NINCDS, especially information relating to diagnosis, treatment and prevention of diseases of the brain and central nervous system. The Center is producing reviews of various clinical problems of interest to the Government, bringing together the relevant clinical knowledge as it applies to the problem. These reviews may focus on an entire disease problem as a whole, or on any distinct part of a disease entity. The Center will identify sources of information relevant to clinical neurological problems, including indexing services, abstracting services, periodical journals, books, monographs, etc.

Major Accomplishments: The Center's most innovative product and one that has been received enthusiastically by the approximately 1200 scientists who receive it is the Concise Clinical Neurology Review. This publication provides a one sentence abstract of a number of papers on a single topic. A number of these topics are covered in a single issue of the bulletin. The bibliographic citations are referenced by a number and appear together in a second part of the bulletin. Approximately 375 papers are selected for inclusion each month, based on a review of 940 serials. This publication seems to fulfill a need not otherwise met in neurology. It is produced once every two weeks and has a subscription rate of $28 per year.

Proposed Course of the Contract: This project was terminated on July 31, 1980 due to lack of contract funds.

CONTRACT NARRATIVE
Neurological Disorders Program
October 1, 1979 - September 30, 1980

Title: Establishment of a Research Roster for Huntington's Disease Patients and Families.

Contractor's Project Director: P. Michael Conneally

Current Annual Level of Funding: $105,942

Objectives: To establish a national roster of patients with Huntington's Disease and their families. This roster will serve as a national source of information for physicians and scientists interested in locating Huntington's Disease patients and families willing to participate in experimental studies into the diagnosis, etiology and treatment of this disease.

Major Accomplishments: This contract has been in effect for about 10 months. Contractor has developed a questionnaire and has begun to collect names and pedigrees. Contractor has also provided appropriate pedigree from roster for major tissue collection research project.

Proposed Course of the Contractor: This program is under the surveillance of an NINCDS project officer and his performance is under continued review.

Demyelinating and Sclerosing Disorders

The demyelinating and sclerosing disorders sub-program includes grant support for Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS), and for research directly relevant to these disorders. As of July 2, 1980 there are 94 active grants, including 6 MS, 1 ALS, and 2 ALS-MS research program projects. Four of the "centers" are due for competing renewal in FY 1981, three in FY 1982, one in FY 1984, and one in FY 1985. Total cost expenditures in support of this research is $ 12,297,508. A total of 70 applications were received and 51 were approved, of which 23 new and 14 competing renewals were funded with a total cost expenditure of $ 2,431,889 for new research grants and $ 4,455,973 for competing renewal grants.

MULTIPLE SCLEROSIS

As a consequence of Congressional interest, the Report and Recommendations of the National Commission on Multiple Sclerosis was issued in 1974. The Neurological Disorders Program of the National Institute of Neurological and Communicative Disorders and Stroke continuew to implement the Commission recommendations.

As of July 2, 1980, in the Multiple Sclerosis (MS) sub-program, 35 grants were active, including 6 MS and 2 ALS-MS research program projects.

Three of these "centers" are due for competing renewal in FY 1981, three in FY 1982, one in FY 1984, and one in FY 1985. Total costs expenditure in support of these activities is $ 7,871,756. A total of 29 applications were received. Twenty were approved, of which 7 new and 7 competing renewals were funded with a total costs expenditure of $ 1,358,443 for new research and $ 3,737,723 for competing renewal grants.

Multiple sclerosis is one of the more common chronic neurologic diseases in the United States. This disease characteristically afflicts young adults and consequently the burden on the patients and their families is multiplied in terms of societal losses.

Myelin, the protective sheath normally present around most nerve fibers is destroyed in multiple sclerosis. Characteristically this occurs in patches, separated one from the other, and at unpredictable times. This process is associated with scar formation and hardening (sclerosis). The areas of demyelination, scattered in the brain and spinal cord, are often correlated with symptoms such as double vision, decreased vision, inability to maintain balance, numbness, or paralysis, tremor, nystagmus, and speech and elimination difficulties. There is lesser involvement of the nerve fiber itself.

The cause of MS is not known but recent observations have provided new and potentially significant insights into possible etiologies and pathogeneses. Epidemiologic studies indicated high and low prevalence areas for MS. Studies of migrant populations strongly suggest that MS is acquired in childhood although the clinical disease is not manifested until adult life.

While this information was being uncovered, the concept of neurologic disease due to "slow virus" infection with apparent incubation periods of months or years was developing. The idea that MS might possibly be a viral disease with a long incubation period was an attractive hypothesis supported by the blending of the fruitful MS epidemiologic studies with the knowledge that the spongiform encephalopathies (including human Creutzfeld-Jakob disease) were transmissible, and also that other chronic neurologic disease of man such as subacute sclerosing panencephalitis (SSPE) and progressive-focal leukoencephalopathy (PML) were directly associated with virus infections.

It is presumed that a viral agent establishes a latent infection which periodically becomes activated leading to myelin destruction. Whether this is the direct effect of the virus or a non-beneficial immunologic reaction, possibly provoked by a secondary viral infection or a nonspecific inflammatory response is not known. The relationship between viral infection and subsequent alteration of the immune system is being intensively investigated.

The possibility that MS may be due to a dysimmune state continues to be a prime consideration in the pathogenesis of the disease. The parallel drawn between animal models of experimental allergic encephelomyelitis, and most recently with relapsing EAE, which mimics MS both clinically and pathologically, has found support in recent studies which demonstrate altered immunological findings in the human disease.

There has been increasing interest in models of virus-induced demyelination during the past few years. Such interest has been stimulated by the current belief that the pathogenesis of MS may in fact be based on combined viral-immunopathologic mechanisms. The study of animal models of virus-induced demyelination is important as it allows dissection of the various facets of demyelination, i.e., morphologic, virologic, immunologic, and biochemical which are not easily studied in human material. These models are among the very few in which a combined viral-immunopathologic mechanism of demyelination appears operative and therefore may have relevance to the human disease, multiple sclerosis.

One animal model of virus-induced demyelination used to investigate the morphological and immuopathological features of myelin injury is Theiler's virus encephalomyelitis which is being studied at Northwestern University as well as in other laboratories. This model is characterized by viral persistence in CNS tissue and by chronic primary demyelination in the spinal cord. Immunosuppression studies demonstrate that demyelination in this model is probably immune-mediated.

Little is known about the ability of virus to infect and produce disease of the oligodendrocyte (the cell responsible for the production of myelin). Furthermore, the factors in the sera of patients with MS which can demyelinate myelinated cultures _in vitro_ are not well characterized. The extent to which remyelination occurs in MS and the role of immunologic or other factors which might inhibit remyelination are unknown.

The neuropathologic research supported at Albert Einstein College of Medicine has been interdisciplinary and largely directed towards the elucidation of immunopathologic events implicated in the pathogenesis of the demyelinated lesion in MS. Foremost in recent achievements has been the continued development and successful application of their model of chronic relapsing experimental allergic encephalomyelitis (EAE). This condition, inducible in inbred Strain 13 guinea pigs with a single inoculation of whole CNS tissue, possesses striking clinical and pathological similarities to the human disease. During the current grant period, the investigators explored the feasibility of monitoring the clinical, structural and immunologic (lymphocyte population dynamics) parameters in this animal model during the relapsing course and have related the findings to the situation in MS. This work reveals that these parameters fluctuate with disease activity in a manner reminiscent of MS. Furthermore, in view of an increasing interest in myelin basic protein (MBP) therapy in MS, they found that MBP successfully prevented the development of this chronic disease and that this suppression might be related to concomitant increases in certain subsets of circulating lymphocytes. Surprisingly, it was also shown that the suppression was permanent since a second challenge of suppressed EAE animals with the nervous tissue antigen failed to elicit disease. CNS repair was also enhanced in suppressed animals. On the other hand, unsuppressed guinea pigs developed new disease after a second challenge. With the initial onset of signs of EAE, it was observed that the T-cell population of circulating lymphocytes decreased significantly. By a subsequent novel experiment, they showed that this dramatic decrease in circulating T-lymphocytes was matched by the appearance of similar T cells within the CNS, suggestive of lymphocyte migration to the target organ. Of significance to the MS situation is the possibility that MBP administration to chronic EAE animals prevents or alters the migration of such cells to the CNS and at the same time causes the generation of a population of cells with suppressor activity within the circulation. The application of this combined clinical, pathological, and immunological approach to chronic EAE represents one major advance in the understanding of possible pathogenetic events in MS.

Other achievements in this laboratory have included: a) the production and characterization of a specific antiserum to the cell which produces and maintains central myelin, the oligodendrocyte, to be used in future immunocytochemical studies of the behavior of this cell type during demyelination; b) investigation of the possible role of an anti-oligodendrocyte antibody in the course of MS by a series of carefully controlled experiments which showed that anti-oligodendrocytes factors in the serum of MS subjects are not specific to MS, do not represent specific antibody, and do not correlate with disease activity; c) experiments using cultures of living CNS and PNS tissue exposed to demyelinating antiserum from animals sensitized against whole CNS and PNS tissue. This approach has been followed for many years in this laboratory in collaboration with others, and permits the investigators to observe the effects of selected factors, e.g. serum, in the absence of a host immune system. Recent findings have shown that complement-depleted anti-CNS or anti-PNS serum will cause a unique proliferation of CNS or PNS myelin, respectively, in vitro. This is evidenced by the apparent stimulation of the myelinating cells to proliferate copious amounts of redundant myelin which has a unique ultrastructure. Ongoing work along these lines will attempt to characterize the serum factor(s) responsible for this unusual behavior of the myelinating cell; and finally, d) experiments to localize and characterize immunoglobulins and viral antigens within the CNS of MS subjects. While this approach provides one promising avenue by which to demonstrate its presence, specific factors in MS have not yet been found.

Since MS appears to be a uniquely human disease, every possible effort must be made to study the disease in man. This requires the ready availability of patients with MS and the interaction of a group of investigators capable of multidisciplinary approaches. In such a collaborative program, various tissue are readily available for study when needed. Blood, cerebrospinal fluid, and autopsy specimens can be examined immediately and do not have to be preserved by procedures which could lead to irreparable damage of a potential MS agent, and immediate availability makes possible studies of cell-mediated immunity. Therefore, extensive programs are built on our present knowledge using newer virologic, immunologic and central nervous system culture techniques.

However, parallel and more wide ranging studies must be carried out in animal models which permit addressing such questions as the neurotropism and potential for damage to the ologodendrocyte or myelin by viruses, the immunologic response to viral infection, studies of immune compartmentalization which require analysis of brain tissue, and studies of the immunogenicity of myelin lipids. Techniques and knowledge which arise from these studies can be applied to studies performed with human material. These are the research themes of the scientists at the University of Pennsylvania and the Wistar Institute and of several other MS clinical research centers.

Numerous physiologically or pathologically active molecules such as certain hormones (insulin), growth factors (Epidermal Growth Factor, Nerve Growth Factor), neurotransmitters, toxins (diphtheria toxin, cholera toxin, tetanus toxin), lectins, etc. bind with high affinity to specific plasma membrane receptors. The mechanism of action of these molecules is not yet understood but it is reasonable to assume that the initial binding of a molecule and its receptor, the subsequent redistribution in the plane of the plasma membrane of molecule-receptor complexes, and the uptake (endocytosis) by the cell of the molecule-receptor complexes are linked with the initiation, propagation, and possibly with the termination of the physiologic or pathologic effect.

Investigators at the University of Pennsylvania have focused on the endocytosis of various molecules (anti-immunoglobulin antibodies, lectins, cholera toxin) which bind to corresponding plasma membrane receptors of lymphoid cells or neurons. They found that these molecules undergo endocytosis in the general area of the Golgi apparatus and specifically in a system of vesicles and cisternae which are positive for acid phosphatase, the so-called GERL (Golgi-Endoplasmic Reticulum-Lysosome). The functional implications of this unusual pathway of endocytosis are being studied. They believe that this pathway might serve either the recycling and re-utilization of receptors or the special degradation of plasma membrane moieties. They are conducting experiments which will clarify the role of endocytosis of receptor-ligand complexes in initiating the cell response to a toxic molecule (ricin) or to a toxin which mimics hormonal actions (cholera toxin). They believe that these studies on the dynamics of plasma membrane are basic to many problems of human neuropathology. Neurons and glial cells are characterized by an extraordinary high ratio of cell surface to cell volume. Cells surfaces must play a key role in physiologic and pathologic processes. Diseases such as human or experimental myasthenia gravis, diabetes mellitus, or the various forms of receptor deficiencies of low density lipoproteins (LDL), serve as examples of the relevance of cell surfaces in general and of receptors specifically, in pathologic processes.

Experimental allergic encephalomyelitis (EAE),has long attracted the attention of scientists. It can be induced in a laboratory animal by injection of nervous tissue or basic protein (BP), a component of myelin. While not the perfect animal model of human MS, it is considered highly relevant to the fundamental research in the demyelinating diseases.

Research at the Wayne State University is focused primarily on the mechanism governing immunologic tolerance to EAE. Normally, the body does not respond immunologically to autologous antigens, a phenomenon known as "self-tolerance." EAE is an exception, since the host can be induced to respond to MBP. By immunizing animals with BP in Freund's adjuvant (which enhances the immune response), self-tolerance can be readily broken down. The immunized animal produces self-reactive-T-lymphocytes which are specific for BP. Since BP is a major protein component of myelin, these lymphocytes (effector cells) bind to and destroy myelin in the CNS, and the animal becomes paralyzed.

Since self-reactive lymphocytic effector cells can be induced by appropriate immunization, it seems clear that a regulatory mechanism controls immunological self-reactivity. The immunoregulation of EAE in inbred Lewis rats has been the thrust of this group's recent research activity They have found that suppressor cells regulate EAE and have determined the requirements for the induction of these cells. Suppressor cells are induced by injecting rats with BP in a nonimmunogenic form i.e., without adjuvant, and EAE is not produced. The suppressor cells localize in lymph nodes and spleen and have been identified as a subpopulation of T-lymphocytes, although there is some evidence that macrophages may also function as suppressor cells. The suppressor T-lymphocytes appear to prevent the induction of disease-inducing effector cells in this model system.

One implication of this finding is that the functional inactivation of suppressor cells may lead to the appearance of effector cells which in turn cause demyelination. This could explain the phenomenon of human demyelinating diseases.

Physiologic regulation of the immune response is thought to be due to the interaction of effector and suppressor cells coupled with an array of soluble factors. A group at Washington University has proposed that one underlying cause for autoimmune effector cell expression is the improper regulation of the induction events that cause cells to differentiate to the effector cell stage. One suggestion, from a conceptual point of view, is that direct immunologic control of effector cells is not part of the regulatory repertoire, and that control of effector cells is regulated at developmental stages prior to effector development (plasma cell, cytotoxic cell, etc.). One could argue that it is more reasonable to regulate a response by preventing effector cell development than by trying to control extensive numbers of effectors.

It is now feasible to investigate this concept of differentiation and control by evaluating relevant inductive, suppressor, and expressor cell interactions in a well studied animal model of autoimmunity, such as EAE. The report that small numbers of lymphocytes readily transfer paralytic EAE makes this model attractive for the investigation of immune control of the autoimmune cell. Cell transfer of paralytic EAE by spleen cells is achieved following an obligatory step involving exposure of sensitized lymphocytes to either specific antigen or stimulation *in vitro*. Observations based on this disease-transfer model has led to the postulate that the cells responsible for initiation of disease in the recipient are terminally differentiated, and as such are not controlled by any suppressor cell population. Moreover, these transferred cells do not induce suppressor activity following transfer to the recipients. The population of cells that is directly responsible for disease initiation are called EAE effector cells EAE(E).

Since transfer of paralytic disease is now readily accomplished, it is possible to study this model of autoimmunity in the rat in terms of the disease process initiated by either active or passive disease-producing mechanisms. In addition recovery from induced EAE normally occurs in the rat so that studies of autoimmune recovery mechanisms following active or passive disease are also possible.

However, transfer of EAE across allogeneic barriers does not lead to detectable signs of EAE. Additionally, although parental (P) to F_1, and F_1 to F_1 transfer of disease is readily accomplished, transfer from F_1 to P has been uniformly negative. These observations of restriction in the transfer of an autoimmune disease, coupled with the observation that the EAE(E) population is apparently not regulated by suppressor cells and does not induce a suppressor cell response in animals that recover from passive disease, indicate that EAE represents a novel system for the study of cell interactions in autoimmunity that can be evaluated within the concepts of established immunologic regulation.

Since the production of EAE transfer effective cells *in vitro* is dependent upon exposure to neuroantigen *in vivo* and subsequent *in vitro* cultivation, this transfer system provides a model for the study of cell regulation under conditions where intervention at either the *in vivo* or *in vitro* steps is available. It is also important to emphasize that the standard assay in the EAE system of autoimmune regulatory events does not suffer from problems of interpretation since the endpoint in these analyses is overt paralytic disease and not the histopathologic criteria which have formerly been the normal assay of transfer of EAE. Therefore, any manipulation during *in vivo* induction or *in vitro* cultivation can easily be tested for biologic significance *in vivo* (paralytic disease) and the manipulations placed in proper perspective.

At present, the EAE transfer system is inadequately understood in the areas of, a) the role of the donor in providing EAE(E) cells that have the obligatory requirement of *in vitro* culture for acquisition of transfer effectiveness, b) the cell interactions and conditions *in vitro* that are required for the development of the EAE(E) population, and c) the role of the recipient in development of passive EAE in terms of recipient-cellular participation, regulatory events, and specific and nonspecific participation in the disease process itself.

The observation that lymphoid cells from antigen-sensitized donors exposed *in vitro* to antigen or mitogen provide effector cells (expanded?, conditioned?, recruited?) that are functional *in vivo* is not limited to EAE and may be a more generalized phenomenon than initially appreciated. An experiment demonstrated the passive transfer of specific resistance to Listeria monocytogenes infection by cells generated by conditioning *in vitro*. In these experiments, spleen cells from Listeria-immune mice were treated with Con A or Listeria antigen *in vitro*. They consequently obtained a population of cells that is 100 times more efficient in mediating passive protection of lethal Listeria challenge in cell transfer recipients. The mouse-Listeria protection model appears to have *in vitro* requirements similar to those observed in the rat-EAE model under current investigation. Moreover, recent reports suggest that tumor immunity can be enhanced by "*in vitro* treatment" of lymphoid cells with mitogen or tumor antigen. In these studies it would appear that the *in vitro* treatment of the lymphocyte population leads to a population of tumor specific cytotoxic lymphocytes that are either increased in number or have become individually more efficient as effector cells. Additionally, it would appear that these cells taken from culture are not affected *in vivo* by host suppressor cells. Together, the observations made in transfer of EAE with "conditioned" effector cells, and the transfer of protection to Listeria, as well as the information from recently published data on the transfer of tumor resistance, point to the concept of "expansion" of biologically significant effector cells *in vitro*. This in turn suggests that a critical evaluation of the nature of the effector cells is warranted.

A finding of considerable potential importance has resulted from the collaborative effort between Duke University Medical Center and the Northwestern University Medical and Dental School. Because of their special expertise in immunochemistry and radioimmunoassay developed in the area of myelin immunology under earlier grant support, an attempt was made to explain why baby rats are unusually resistant to the induction of EAE. Could it be that this display of tolerance is due to the presence of the antigen, MBP, in the circulation of these rats that dampened their immunologic response to injections of the antigen? The team at Duke University looked for immunochemical evidence that this was so in samples sent to them under code from Northwestern University. They found some samples with MBP in them and others without. When the code was broken, the MBP-positive samples were from the suckling rats and the MBP-negative ones were from adults.

However, with increased sensitivity of the method, they found definite evidence of serum MBP at very low levels in the adult also. Pursuing the analysis still further, they began accumulating indirect evidence that the serum MBP was not the intact form of the protein as it exists in the myelin sheath, but in the form of circulating fragments. Sometimes one fragment would appear and sometimes another. Infrequently all fragments were present. Currently they are isolating and purifying some of these fragments in order to have direct evidence for their existence and hopefully to pinpoint their place in the MBP molecule. The difficulties they face stem from the extremely small concentrations involved. The amount of MBP fragment in adult blood, for example, may be so small that it would take 50 gallons to yield the equivalent of a 5-grain aspirin tablet.

Thus, what began under the aegis of an NINCDS grant as an immunochemical analysis of myelin architecture some seven years ago has become an immuno-chemical search for myelin fragments in the circulation. Consequently, the assumption now is that some of the major events that determine whether "neuroautoimmune reactivity" spills over into the brain itself, take place in blood.

An investigator at University of Maryland deals with the problems of how myelin membranes (layers of cell membranes which wrap around the axon of the neuron) are destroyed by immune mechanisms operative in diseases like MS. Specifically, he wants to know how humoral immune factors such as antimyelin antibodies and complement can damage the myelin. The complement system (14 proteins present in blood and body fluids) is known to damage the lipid layers of cell membrane when they are "activated" by antigen-antibody complexes or by various microorganisms. Experiments are being designed to determine whether these "membrane-attack" complement systems can insert their peptides into the myelin membrane when they are "activated" by anti-myelin antibodies, thus creating transmembrane pores, or how they destroy the membrane by removing lipid from the membrane. It is also possible that both mechanisms may operate together.

Most of the work on neural tissue cultures is concerned with the Schwann cell - the principal accessory cell in the peripheral nervous system which is responsible for elaboration and wrapping of the insulating sheath of myelin around certain nerve processes. The objectives of investigators at the California Institute of Technology are to understand at a molecular level, how the nerve is able to induce the Schwann cell to make myelin, and how the division of the Schwann cell is controlled. They study these questions in tissue culture because they have devised a way of obtaining the cells in a highly purified form. These studies are of relevance for diseases such as multiple sclerosis which involve demyelination. If one can understand how a myelinogenic cell is triggered by the nerve to make myelin, one might be in a much better position to suggest ways to promote repair of demyelinated areas. The studies are also of basic importance for our understanding of surface mediated cell-cell interactions where one cell affects gene expression (i.e., induction of myelin proteins) in the second.

The major thrust of the research at Emory University is (1) to investigate the synthesis, breakdown, and turnover of basic protein (BP) in myelin and related membranes, and (2) to investigate the possible functions of this membrane protein in myelin.

A most important finding is the clear demonstration of a stable myelin in brain which is synthesized only in the young rapidly myelinating animal. This stable myelin core has been separated from the total myelin by sedimentation in a sucrose density gradient. The specific activity of the myelin proteins in this fraction does not change during the adult life of the animal. This is the first time a stable myelin fraction has been demonstrated. In the past it has only been shown that the labeled amino acids remain in the total myelin, a result which could be explained by reutilization of labeled amino acids. This explanation is not in agreement with the results of their experiments. The information obtained in studies of myelin membrane damaged by the complement system could contribute directly to the membrane modification studies. A considerable amount of work in this field with sheep erythrocyte membrane and with liposomes (artifical membranes made with known chemical components of lipid) was done. Through these experiments, we have learned that certain unsaturated lipid is more susceptible than its saturated lipid counterpart, and lipid with longer chain length behaves like the saturated lipid when attacked by complement. Furthermore, cholesterol in the membrane protects and reduces the extent of damage.

Studies are now exploring ways of modulating the myelin lipid composition to learn what types of chemical or physical changes in the membrane can reduce the extent of myelin damage under these circumstances. It is well known that the nature of lipid in the diet can directly influence the chemical composition of cell membrane lipid. Thus, dietary lipids could affect the effector phases of demyelinating diseases. The understanding and prevention of the initiating phases of these diseases are much more remote goals of these studies.

Data is being collected at Yale University on the glycosphingolipid composition of normal and pathological nervous tissues. The latter include brain tissues afflicted by multiple sclerosis and "slow viruses". Special emphasis is being placed on sialic acid containing glycosphingolipids (gangliosides), and their structures and metabolism as related to the maintenance of membrane integrity.

An investigator at the University of Maryland also is working on elucidation of the details of the lipid intermediary pathway for the glycosylation of asparagine residues in membrane glycoproteins in the central nervous system. They have also begun to study the enzymatic sulfation of membrane-associated glycoproteins and proteoglycans in brain. The objectives of the second phase of this study will be to solubilize and purify the sulfotransferases to study their properties and specificities. The major focus now with regard to lipid-mediated glycosylation is to determine the role of dolichol kinase and a membrane-associated phosphatase that dephosphorylates dolichyl monophosphate.

The studies on enzymes of phosphoinositide metabolism should provide basic information on factors which influence the metabolism of these substances. This is particularly true with respect to phosphatidic and phospho-hydrolase, which, considerable evidence suggests, may catalyze a key rate-limiting step in synthesis of major cell phospholipids and triacylglycerol.

Studies of the interaction of rhodium (II) carboxylate with a well characterized membrane such as the human erythrocyte membrane, should shed light on the mechanisms of action of these complexes which gives rise to their antitumor properties. Since the structure of the carboxylate ion can be varied, the development of novel specific probes for membrane sulfyhydryl groups is a realistic goal.

Understanding of the chemical architecture of myelin and the factors maintaining myelin stability is of importance. The research program at the Eunice Kennedy Shriver Center for Mental Retardation has been specifically directed to the chemical characterization of the bovine white matter proteolipid apoprotein and to the determination of its primary sequence. A major problem which must be dealt with is the tendency of the protein and the peptides derived therefrom to aggregate and precipitate.

These studies are basic to an understanding of the chemical architecture of the brain and, in particular, of myelins. Proteolipid protein is quantitatively the major protein of CNS myelin and a study of its primary structure should provide a basis for understanding the unusual solubility properties of the protein, its function within the myelin membrane and its interactions with other myelin components. These studies relate to fundamental problems in membrane biology as well as to the specialized function of myelin as an insulating membrane. They should contribute to an understanding of the structural factors which maintain the integrity of the myelin sheath and the abnormalities which affect myelin stability in demyelinating diseases, including multiple sclerosis and diseases of genetic and environmental origin.

Another aspect of this proposal deals with the practical problem of quantitatively detecting antimyelin antibodies in the serum or cerebrospinal fluid (CSF). The only method now available involves newborn mouse central nervous tissue explant culture. Large quantities of CSF or serum are needed in order to observe myelin destruction in this system. The culture technique is difficult (it takes about a month) and the results are not quantitative. Therefore, these investigators seek to develop assay techniqes with liposomes made with extracted myelin lipid. The extent of trapped markers released from the liposomes when they are treated with antimyelin antibody and complement should reflect the titer of antibody present in the test sample.

The work on a glial growth factor may be important for an understanding of the glial proliferation that is a prominent response to injury in the central nervous system, and for an understanding of those aspects of neurotropism that affect proliferation of nonneuronal cells. One dramatic example of this is the effect of nerves on controlling limb regeneration in lower vertebrates - an effect which may be mediated in part by an uncharacterized basic protein in brain. The glial growth factor may be relevant in these areas as well as to more basic aspects of growth control.

Understanding of the putative autoimmune mechanisms involved in multiple sclerosis (MS) is of the utmost importance. An investigator at the University of California is attempting to identify and isolate cell surface antigens on oligodendrocytes which are reactive with sera from patients with MS. He is also studying the *in vitro* cellular immune reponse to oligodendroglial cell antigens of patients with MS, patients with other neurological diseases and of normal control subjects. Bovine oligodendrocytes are isolated from white matter by trypsinization, followed by screening and sucrose density gradient centrifugation. Oligodendrocytes isolated by this manner exhibit the biochemical and morphological characteristics associated with this cell type. The cell preparations are used to screen MS sera for reaction with oligodendrocytes by immunofluoresence. All sera used are absorbed with bovine liver, kidney, spleen, heart, glutaraldehyde-fixed serum proteins and bovine myelin. Sera from five MS patients in relapse, five with progressive disease and five normal subjects have been screened and no specificity was found. It was observed that there is only minimal binding to the bovine oligodendrocytes of IgG from either MS or normal sera. These results are in direct contrast to the observations of another scientist.

Utilizing immunoprecipitation techniques, an MS relapse serum was found that precipitated several protein species which were absent in control gels. Four bands were found which had molecular weights in the 20,000 to 40,000 range.

The effect of macrophage secreted proteases on myelin degradation are investigated as one possible mechanism of demyelination. Comparative X-ray diffraction studies of mature, immature, and abnormal myelins derived from various species are being carried out. Nuclear magnetic resonance (NMR) spectroscopy is being used to study interactions between MBP and myelin specific lipids. New techniques and instrumentation are being developed to study membrane structure and membrane models. The demyelinating effect of serum from MS patients and EAE is also being analyzed.

The recently developed oligoclonal immunoglobulin assay can confirm MS diagnosis in about 90 percent of cases. However, there is great interest in developing even more sensitive and reliable diagnostic tests for MS. A highly sensitive radioimmunoassay is being used to assess demyelination and myelination using nucleotide rich material (NRM) found in the CSF which is unique to MS patients. Further, an attempt is being made to verify the presence of neuroelectric blocking factor(s) reportedly found in serum obtained from patients with MS.

A group at Johns Hopkins University and others have reported that basic protein appears in the cerebrospinal fluid (CSF) of MS patients undergoing an acute attack. The presence of myelin basic protein in the CSF of MS patients undergoing acute attacks may have practical significance in that it may assist in the early diagnosis of MS and permit monitoring of the activity of the disease in patients with confirmed MS. Myelin basic protein assay in CSF may also prove to be a useful tool for measuring response to therapy.

On a more theoretical level, characterization of the properties of this spinal fluid myelin basic protein may shed light on the mechanism by which the myelin was damaged or degraded initially. Currently there is active investigation into the properties of this myelin protein in the CSF. Some laboratories have detected a fragment of the basic protein, wheras others have evidence for a large molecular weight material, and an electron microscopic investigation of CSF sediment reveals whole myelin fragments. These data indicate that material containing antigenic sites distributed over the entire basic protein molecule is present in the CSF.

It was reported that the CSF from MS patients has a myelinotoxic effect. Studies are being conducted to assess its diagnostic potential for MS. Parameters of altered cell-mediated immune responsiveness are being correlated with the clinical course of MS patients in an attempt to develop a more specific diagnostic test for MS. Idiotypic antibodies in the CSF are also being investigated as markers of MS. An attempt is being made to standardize solid phase radioimmunoassay for brain phospholipid protein (PLP) as a measure of MS activity.

Serum and brain tissues from MS patients and appropriate controls continue to be collected at the MS center at University of California, San Francisco. The quantitation of IgG, and IgG antibody specificity, identified from these sources, continue to be the primary activities. The laboratory is able to detect antibodies to numerous common viruses by standard and radioimmunological techniques. Specimens from the United States and Japan are analyzed. Some oligoclonal bands in the CSF of patients with MS and subacute sclerosing panencephalitis appear to contain antibodies which react with both measles virus and myelin basic protein. Because of the serological and epidemiological evidence linking measles virus to MS, evidence for persistence of the virus genome in MS tissue is sought.

ACTH and steroids continue to be used in the treatment of exacerbations of MS. Other pilot studies are exploring immunosuppressive therapy with azathioprine, prednisone with azathioprine and cyclophosphamide. The immunopotentiating agent, Levamisole, has been investigated. A current study is attempting to assess the value of L-tryptophan and electric stimulation for improvement of certain signs and symptoms. The management of the patient's emotional status, and the effects of tension, frustation, and depression on the endocrine system have received some attention.

The Institute support of reserch in endocrinology is relatively modest. These studies address hormonal regulation and control mechanisms, hormone binding, hormone receptors, hormone analogs, biosynthesis, inhibitors, and metabolism of peptides,neurotransmitters, and immunoglobulins. Moreover, hormonal studies of MS patients are very limited. Our Institute's financial support data indicates relatively little activity in this area of research in the U.S.

Research efforts are focused on the development of hormonal responsiveness in reaggregate cultures. Included in the hormone response studies are investigations concerning identification and characterization of alpha and beta-adrenergic hormone receptors, dopaminergic receptors and prostaglandin receptors.

Investigations at the University of California, Los Angeles during the last year have expanded knowledge of environmental, familial-genetic, and immunologic factors associated with the pathopoiesis of MS. Studies of the prevalence of MS among American-born migrants to Los Angeles and Seattle from low and high prevalence areas within the United States have suggested that the risk of MS increases with the age at migration up to at least age 20. This effect was observed regardless of the area from which these individuals had migrated and whether they migrated to either Los Angeles or Seattle. The prevalence was highest in the groups migrating from high prevalence areas to Seattle (a high prevalence area) and lowest in the groups migrating from low prevalence areas to either city.

To investigate the reasons for this "age-at-migration effect" a case-control study was done on MS patients and matched neighborhood controls not born in Los Angeles. MS patients were found to have had almost twice as many changes of residence as matched controls. This increased mobility among patients may reflect a greater opportunity for exposure to a single etiologic factor or for multiple exposures acting on a susceptible host. No differences were found between MS patients and controls in exposure to either small or large dogs.

The question of susceptibility was examined by studying the distribution of histocompatibility antigens in families with more than one case of MS. A preliminary study of 13 multiple-case families indicated that a single haplotype was associated with MS in all families, but that no single HLA allele was associated with MS in all of these families. Some non-affected members of these families also shared the haplotype associated with MS indicating that penetrance was less than 100 percent and suggesting that additional factors beyond genetic susceptibility were necessary to cause clinical expression of the disease. Subsequent log of the odds (LOD) score analysis of a total of 45 multiple-case families supports the hypothesis of genetic susceptibility.

Studies of immunologic responses among patients and cohabitant controls confirm that MS patients have higher antibody titers to measles than controls, but also showed patients to have less competent cell-mediated responses to measles according to the leukocyte migration inhibition test. Measles antibody titers and impairment of cell-mediated immunity to measles were lower among patients with the DRW -2 allele than among those patients without this allele. Humoral immunity to cytomegalovirus and herpesviruses 1 and 2 were similar between cases and cohabitant controls. Cell-mediated immune responses to streptokinase-streptodornase (SK-SD) were not impaired. These observations suggest that the aberrant immune responses were specific to measles or an antigenically closely related virus(es). The lesser degree of immunologic impairment to measles antigen among patients with the DRW-2 allele and the higher frequency of this allele among patients may reflect selective survival mechanisms.

Studies are currently underway to: 1) investigate factors which cause genetically susceptible individuals to develop MS, 2) detect changes in immunologic responses in relation to clinical changes, 3) determine immunologic responses to other viruses, particularly myxoviruses, and 4) compare survival, rate of progression and disability among patients in high and low prevalence areas.

AMYOTROPHIC LATERAL SCLEROSIS

As of July 2, 1980 the Amyotrophic Lateral Sclerosis (ALS) sub-program had 11 active grants which includes one ALS research program project due for competing renewal in FY 1981. The total cost of these research activities is $903,049. When the two ALS - MS "centers" are also included, the number of active grants is 13, for a total cost of $2,576,188. Fourteen applications were received and 7 were approved. Six of these are new and cost $391,411.

Amyotrophic Lateral Sclerosis (ALS) is one of the motor neuron diseases (MND). These diseases are characterized by impairment of the function of motor nerves controlling voluntary muscles which results in progressive muscle paralysis. The cause(s) of the nerve dysfunction and degeneration is not known.

The clinical picture is characterized by muscle weakness, fasciculations and wasting associated with hyperreflexia. Speech and swallowing difficulties are frequently encountered. Sensory changes are not a characteristic part of this disease. It is of particular interest that cranial nerves III, IV, and VI are, with rare exceptions and very late in the disease, spared. The same is true of bladder and bowel function. Urinary incontinence is a rare phenomenon, and sexual function is preserved.

Motoneuron disease usually occurs sporadically in the population with a prevalence which has been estimated to be 2-7/100,000 population. Although statistics are sparse and incomplete, it appears that about 4,000 new Amyotrophic Lateral Sclerosis (ALS) cases are diagnosed each year, extrapolated from the most recent study. Approximately 5 percent of the patients have a family history of the illness, and sometimes an autosomal dominant pattern of inheritance is seen. Males are more affected than females, with a preponderance of 1.6-2 to 1. Several retrospective studies have shown the mean age of onset to be between 46 and 56 years. The disease is progressive and disabling but most patients may live 3 to 5 years, whereas others reach a plateau and live 10 years or rarely longer.

AlS has a fairly uniform world wide distribution with some exceptions. Geographic areas of high incidence include the Kii peninsula of Japan, Guam and the Mariana Islands, and the Kepi region of New Guinea. A low prevalence has been found in Mexico.

At present, there is no effective treatment for ALS. Symptomatic relief of excessive salivation may be achieved pharmacologically. Past treatments which have proven ineffective include neurotoxin, corticosteroids, immunosuppressive regimens, immunostimulatory drugs, transfer factor, and plasmapheresis.

Laboratory studies are helpful in the diagnosis of MND. Electromyography shows widespread fibrillations associated with giant polyphasic potentials and fasciculations. Motoneuron conduction velocities are typically normal. Muscle biopsy may be helpful in establishing the diagnosis. Serum and cerebrospinal fluid (CF) protein, sugar, and electrolytes are usually normal. Serum creatinine phosphokinase (CPK) as well as other muscle enzymes may be increased to two and three times normal in about half of the patients.

Examination of the central nervous system (CNS) discloses selective degeneration and loss of the large motoneurons of the ventral horns of the spinal cord and brain stem nuclei. The nuclei of III, IV, and VI cranial nerves, and the medial sacral nucleus (S2) motoneurons in the spinal cord are characteristically spared. These findings correlate with the clinical signs. There is secondary degeneration and gliosis of crossed and uncrossed corticospinal tracts. The posterior columns are spared except in familial cases. In ALS the earliest axonal loss occurs in the long peripheral nerves and in the cortico-spinal tracts, initially in the zone most remote from the cell body. This pattern of "dying-back" degeneration is probably a reflection of failure of the cell machinery to provide for its most distal parts. The other observation, emphasized recently, is the presence of swellings of the proximal portion of the axons. The axonal swelling appears to be an important early lesion in ALS. The swellings, containing large numbers of neurofilaments, are quite commonly identified in the anterior grey matter in classic sporadic ALS and in familial cases, as well as in Werdnig-Hoffmann's disease, a motoneuron disease of early life. The swellings disappear as the motoneurons die, and are rarely seen in end-stage disease when the majority of motoneurons have disappeared. It has been suggested that these swellings are the result of some abnormality in the dynamics of transport of axonal materials. The axoplasmic transport system is important in maintaining the functional integrity of the nerves and the reciprocal interdependence between them and the target cells.

The only other pathological changes which have been described are a variety of "inclusions" and "bodies" within the cytoplasm of neurons from classical and Guamanian ALS cases. Some of these are due to neurofibrillary alterations taking the form of ring-like or herringbone arrangements. Similar changes are found in brains of patients in their 70's and 80's. Some of the Guamanian patients showed these changes as early as 28 years of age.

The etiology and pathogenesis of MND are unknown. Heavy metal intoxication is one of the more popular suggestions. Lead intoxication may result in a motor neuropathy in the absence of any sensory signs. Organic mercurial compounds have been reported to cause MND in patients poisoned by a fungicide used on wheat. A more recent retrospective study has suggested that a history of exposure to mercury and lead is more commonly elicited in ALS patients than in controls. CSF lead levels have been reported to be higher in ALS patients than in subjects with other neurological diseases (OND) and normal controls, whereas plasma lead levels show a lesser change. It is proposed that the normally efficient "trapping" mechanism performed by the erythroid series in the bone marrow is defective in ALS patients. Another suggestion is that lead is more avidly taken up by ALS than by normal nerves, and transported by retrograde axonal flow, causing neuronal cell body damage. Not all investigators report elevated lead levels, and further analyses are required.

Aluminum has also been implicated. High concentrations of aluminum have been found in certain neurologic conditions such as Alzheimer's disease, progressive encephalopathies associated with industrial exposure, and in uremic patients undergoing hemodialysis. In addition, aluminum experimentally leads to neurofilament concentration in neurons and possibly impairment of axonal transport. This may be important since enhanced aluminum absorption from the intestine occurs with parathyroid hormone administration, and hyperparathyroidism may be associated with MND.

Selenium toxicity has also been suggested. A preliminary report indicates that during a ten-year period, four cases of ALS had been found in a sparsely populated county (population 4,000) in west central South Dakota. The cases occurred in a region where naturally occurring selenium intoxication had been endemic in farm animals. This study has been challenged as not stasticially significant.

It is well known that neurogenic atrophy may be encountered in some metabolic disorders, such as hyperthyroidism, insulinomas, hyperparathyroidism, steroid therapy, and hyperadrenalism. In ALS, however defects of carbohydrate metabolism have been noted on several occasions in ALS patients. Abnormal glucose tolerance, tolbutamide tolerance and subnormal insulin secretion have also been found. Impairment of pancreatic exocrine function has also been reported with decreased neutral fat uptake, mild steatorrhea, and an abnormal response to secretin stimulation. These studies, however, are in dispute.

As mentioned above, neuromuscular dysfunction has been associated with hyperparathyroidism. The recent description of neurogenic atrophy associated with parathyroid adenomas and increased parathyroid hormone (PTH) deserves closer scrutiny. This is of interest since a very occasional ALS patient has been found to have frank hyperparathyroidism and many patients with hyperparathyroidism have a MND-like abnormality. This is particularly important since PTH may increase the absorption of aluminum from the gastrointestinal tract. The association of these numerous toxic and metabolic disorders with a motoneuron-like disease is of great interest. Thus far, however, none of these factors has been found to be definitely operative in classical ALS.

An investigator at the University of Maryland is sudying the mechanism whereby muscle glucose 6-phosphate dehydrogenase (G6PD) is neurally regulated. G6PD is the rate limiting enzyme in the pentose phosphate pathway and is increased in otherwise normal neurones after denervation or application of myotoxic drugs. It had been suggested that the rate of increase of this enzyme is related to nerve stump length. This was recently confirmed, although interrupting axonal transport with vinblastine impregnated silastic cuffs did not cause an increase of this enzyme. A series of studies are now proposed to look further at the relationship of neural influences on G6PD.

The chemistry of motoneurons as it might relate to ALS has recently been reviewed. Anterior horn neurons have a particularly high level of G6PD and hence might have a greater capacity for lexose monophosphate shunt activity than other nerve cells. In ALS, G6PD was found to be normal. Others found that anterior horn cells had a relatively higher level of energy utilization than other spinal cord neurons. Alpha motoneurons appear to be richer in phosphorylase and in lysosomal enzymes than other neurons.

The normal G6PD level in ALS is of interest because of the findings in normal neurones of G6PD three-fold increase following axonal injury and during chromatolysis, as mentioned earlier. The normal G6PD levels in ALS may indicate that the ALS neurons cannot respond to the axonal injury, or that the axonal injury is not primary. A consistent finding in neurones of ALS and progressive muscular atrophy (PMA) patients has been excess lipofuscin, a nonspecific finding seen in many conditions as well as in aging neurons. A decrease in the oxidative enzymes, acetyl cholinesterase, thiamine pyrophosphate, and cyclic AMP and an increase in acid phosphatase was found in the CNS of ALS patients. A histochemical study of MND showed a decrease in two membrane enzymes, ATPase and 5-nucleotidase. This histochemical study also showed abnormalities in the nucleus, suggesting a progressive inhibition of DNA-directed messenger RNA synthesis. Some quantitative biochemical analyses on the spinal cord from a Guamanian ALS patient disclosed normal levels of malic and lactic dehydrogenase, hexokinase, glutamic dehydrogenase, G6PD, and hydrolytic lysosomal enzymes.

Suggestive abnormalities in the biochemistry of putative neurotransmitters have also been described. The spinal fluid of ALS patients has been shown to contain low levels of homovanillic acid (HVA). This was attributed to reduced dopamine synthesis in the CNS since the probenecid-induced accumulation of HVA was also reduced. Following L-Dopa therapy, there was a marked rise in HVA, but no clinical benefit was observed.

Cyclic AMP has also been found to be low in the spinal fluid (CSF) of ALS patients as well as in patients with involvement of spinal motoneurons encountered in other diseases such as spinocerebellar ataxia. Administration of a phosphodiesterase inhibitor to ALS patients resulted in significant elevation of CSF cyclic AMP levels. However, there was no clinical change. ALS patients do not have a low level of CSF cyclic GMP or low serum levels of cyclic AMP or GMP. The low levels of cyclic AMP in the CSF could be due to neuronal death or could reflect an absence of a specific neurotransmitter. The most recent biochemical studies identifed abnormal levels of free amino acids, such as tyrosine and basic and aromatic amino acids in 12 ALS patients. These patients also had statistically significant elevations in CSF total basic amino acids including leucine. These findings are suggestive of defective membrane transport in the CNS.

Neurones relate to other elements by establishing neuronal-neuronal, neuronal-glial, and neuronal-muscle interrelationships. It is postulated that these cellular relationships are important in the synthesis and release of neurotransmitters, the expression and maintenance of receptors, and the generation of trophic factors necessary for the health of the motor unit. In addition to direct connections from the large pyramidal neurons in the motor cortex, the alpha motoneurons in the anterior horns of the spinal cord receive input from group Ia muscle spindle afferents, and from the descending tracts from the vestibular nuclei, brainstem reticular formation, and the red nucleus. The major synaptic input, however, is from the poorly defined spinal cord interneurons. The putative neurotransmitters in the spinal cord have not as yet been defined. Anterior horn cells have receptors for gamma-aminobutyric acid (GABA) and there is good evidence of postsynaptic actions of glycine, alpha-alanine, beta-alanine, taurine, aspartic acid, and glutamic acid. Many studies remain to be done on neuro transmitters in ALS patients, particularly in regard to their synthesis and release, and the state of their receptors.

The questions related to function at the synaptic membrane have not been addressed at all. Reactive changes such as axonal sprouting have been described in

ALS. Axonal sprouting can be the result of inhibition of transmitter release at the presynaptic membrane. Such is the case with botulinum and tetanus toxins, where, following denervation, regeneraion occurs in the form of axonal sprouting from intact nerve terminals.

The questions relating trophic factors which influence the expression of receptors, the release of transmitters, and the general maintenance of neuronal health, have been addressed largely in the developing nervous system. However, in recent years, the mature nervous system has received attention. Changes in the peripheral nervous system, such as physical and biochemical axotomy and interference with neuromuscular transmission and muscle destruction, cause biochemical and morphological abnormalities in both developing and mature ventral horn cells. Axotomy also causes changes in the shape of excitatory postsynaptic potentials of motoneurons and failure of Group Ia synaptic connections. Axotomy has also been found to cause loss of muscarinic receptors and loss of synaptic contacts in the hypoglossal nucleus suggesting that the presence of receptors is necessary for the maintenance of the physical contact between pre- and postsynaptic elements by acting as a trophic influence.

The feedback interplay between muscle and neuron is still to be defined. Some basic work has suggested that the contractile and metabolic characteristics of muscle fibers are tightly coupled with the biochemistry of motoneurons. Fast and slow muscle biochemistry is determined by the motoneuron. Rat motoneurons exhibit changes in the G6PD and acid phosphatase following repeated contraction, and chromatolysis occurs in motoneurons of mice exhausted by swimming. Finally, it was found that the activity of choline acetyltransferase, the enzyme involved in the synthesis of acetylcholine, was significantly greater in combined cultures of spinal cord and muscle cells than in cultures of spinal cord cells alone. The increased activity of this neuronal enzyme is associated with the formation of functional neuromuscular junctions in culture.

The failure of transmitter release, receptor sensitivity, and trophic influences may all depend on intact axonal function. As described previously, the two suggestive findings implicating impaired axonal function in ALS are the presence of filament-rich proximal axonal swellings and the severe degeneration in the lumbosacral levels of the corticospinal tracts and the distal regions of peripheral motor nerves implicating a "dying back" process. In addition to these findings, Dapsone (4, 4-diaminodiphenylsulfone), a drug used in skin diseases and leprosy, produces an axonal disease of motor nerves in humans. Recovery from drug related damage occurs by regeneration of axons and by peripheral sprouting of non-damaged axons. It is suggested that Dapsone causes a "dying back" phenomenon which impairs the soma and axons of the motoneuron.

In experimental intoxication by B,B imidodiproprionitrile (IDPN), in hereditary canine spinal muscular atrophy, and in MND, chromatolysis (a reaction to axonal injury) is a rare finding. These observations have supported the hypothesis, suggested earlier, that neuronal death in MND is secondary to the inability of motoneurons to respond to axonal damage. Again it is not known whether the failure to observe the classical changes of chromatolysis in most cases of MND is due to the failure of the "signal" from the periphery to arrive, due to the inherent failure of the motoneuron to receive and translate the "signal", or may merely indicate that the primary defect is in the cell body.

The IDPN study is designed to examine the pathogenesis and the consequences of neurofilament accumulations in motor axons of rats exposed to IDPN. It appears that defective slow axonal transport of neurofilament proteins underlies the axonal pathology.

Investigations at Johns Hopkins University attempt to understand the ways in which neurons are affected by or respond to disease processes, including traumatic injury, genetic factors, and toxins. The strategy has been to study animal models of human disease using a variety of approaches derived from contemporary neurobiology.

They have used IDPN in dogs and cats to induce axonal swellings. The initial short-term studies reveal striking clinical differences between dogs intoxicated with IDPN and rats similarly treated. They have succeeded in producing chronic disease in dogs by giving IDPN for long periods (9 months or more). It was thought that the large animal model would allow studies that were particularly difficult or impossible to perform in the smaller rat model. Utilizing radiolabeled proteins, they are determing the rates of slow anterograde transport. These studies have proved more difficult in dogs than in rodents. The large musculoskeletal system of dogs virtually precludes rapid removal of fresh tissues without severe disruption of other tissues needed for ultrastructural studies. Radiometric studies in the chronically intoxicated dogs show an accumulation of radioactivity in the ventral roots. The retained radioactivity parallels the distribution of axonal swellings.

Their breeding studies have been successful in producing hereditary canine spinal muscular atrophy in Brittany Spaniels. The colony includes 20 dogs. The disease affects both sexes, and therefore is not sex-linked. Based on their initial studies, the disease appeared to be inherited in an autosomal recessive fashion. The phenotypic expression of the disease varies with the age of onset, progression of the disease, and pathological changes. Three types (I, II, and III) have been recognized: accelerated, intermediate, and late-onset chronic disease. The neuropathology correlates well with the clinical manifestations of disease. Pups with Type 1 form of disease have massive numbers of swellings in the proximal axons, as well as neuronophagia, chromatolysis, and glial bundles in the anterior horns. The latter three features are considered to be characteristic of Werdnig-Hoffmann disease. Virtually every proximal motor axon is swollen and contains maloriented arrays of neurofilaments. Because neurofilaments are carried by slow axonal transport, they have hypothesized that the pathology is due to impairment of the slow axonal transport system. Dogs with the intermediate form of disease have a marked loss of motor neurons with concomitant decrease in the number of axonal swellings. Within the ventral horns, there are empty baskets which once contained motor neurons; in the ventral roots, there are glial bundles similar to those in pups with the accelerated type of the disease.

They have also initiated studies of the neurotoxic effect of two of the commonly used antineoplastic drugs; misonidazole and cis-platinum, which may represent new models of peripheral neuropathy.

An investigator at Mount Sinai conducts experiments to determine the biochemical changes occuring in distal axonal neuropathy caused by acrylamide and methyl butyl ketone. Emphasis is placed on possible changes in lipid metabolism and axonal transport. The effect of these agents on the synthesis of lipids in lymphocyte membranes is also being evaluated. The information obtained from this study may be useful in screening agents for toxicity.

The histocompatibility antigens in ALS patients have been explored in a number of laboratories. HLA refers to all gene products controlled by the major histocompatability complex region which is located on human chromosome 6. Ankylosing spondylitis, psoriasis, multiple sclerosis, diabetes mellitis, and myasthenia gravis have been associated with over-representation of certain HLA determinants with respect to the general population. Numerous reports suggest an increased incidence of various other determinants in motoneuron diseases. There was an increase in A 3 in ALS patients in Boston. In the Glasgow area, an increased incidence of A 2 and A 28 was found. An investigator in Denmark was unable to demonstrate a particular phenotype frequency pattern. Another investigator found none of these phenotype frequencies in Guamanians with ALS, but recently found an association with HLA Bw 35. Thus far, a clear pattern of HLA phenotypes or haplotypes has not emerged in studies of classical ALS patients.

A wide variety of immunologic indicators of disease have been studied. Neutralizing antibodies to polio, mumps, herpes, and influenza viruses were similar in ALS patients and controls. Guamanians with ALS have similar levels of antibodies to herpes, cytomegalo, and Epstein-Barr viruses as compared to age and sex-matched controls. The immunoglobulin levels in twenty-one patients were found to be normal. Five of thirteen patients in this study with Progressive Multifocal Encephalopathy showing no evidence of pyramidal tract involvement, did show elevated levels of serum IgM. The percent serum immunoglobulin in sixteen motoneuron disease patients was higher than in eight controls, but not higher than in six patients with other neurologic diseases.

Immune complexes measured by the ClQ binding assay were demonstrated in the sera of ten of twenty-five ALS, patients. In that study, renal glomeruli from nine of thirty-three ALS cases showed no IgG and C3. The deposited complexes after elution showed no immunologic reactivity to poliovirus. A similar study was done on sera from patients with ALS and Parkinsonism-Dementia (PD) on Guam. Three of the five ALS patients and four of the twelve PD patients showed significant binding of ClQ. Circulating immune complexes were also reported in ten percent of ALS patients using the Raji cell method for detecting immune complexes. There is, therefore, a suggestion that immune complexes are present in the sera of ALS patients but the nature of the antigenic component has not been defined. Skin tests for delayed hypersensitivity are normal. It is stated that a generalized anti-inflammatory response had been noted in ALS patients. Skin testing of Guamanins with ALS and PD to recall antigens showed diminished responsiveness. A lessened response has also been found in patients with bulbar ALS. In contrast to these studies, a whole host of immunologic studies in ALS patients for a variety of antigens such as basic protein, crude brain extract, and purified acetylcholine receptor have been negative. T and B cells have also been found to be normal. Total lymphocytes were reported to be elevated in ALS as compared to controls but not when compared to other neurologic diseases.

Serum factors have also been implicated in producing toxicity in vitro in murine anterior horn cells. In a follow-up study it was recently found that sera from six of twelve ALS patients, one of three normal controls, all three Duchenne muscular dystrophy and one of two spinal muscular atrophy patients were positive. These studies could not be repeated. The factor in human sera which appears to be toxic to rodent anterior horn cells has not yet been identified. The evidence for a viral etiology of MND is not firmly based. There are a number of reasons, however, to implicate viruses in the etiology and pathogenesis of MND. These include the following: 1) There are other noninflammatory, progressive degenerative CNS diseases due to viruses: Progressive multifocal leukoencephalopathy (PML), Creutzfeldt-Jakob disease, and Kuru. 2) ALS patients give a history of antecedent paralytic poliomyelitis at rates up to ten times greater than control patients. 3) Many patients following paralytic poliomyelitis develop a slowly progressive, although for the most part, benign motoneuron disease. 4) A recent study of tissues from ALS patients suggests that there is a defect in DNA directed messenger RNA. A variety of viruses are known to interfere with host cell macromolecular synthesis. These include picornaviruses such as polio, pox, and some paramyxoviruses such as Newcastle Disease virus. 5) A transmissible C-type virus has been found to cause a kind of motoneuron disease in the aging populations of a wild mouse colony. 6) RNA directed DNA polymerase (reverse transcriptase), an enzyme associated with oncornaviruses, has been demonstrated in the brain of Guamanian ALS patients and "normal" controls, but not in American ALS patients. 7) Picorna (polio, coxsackie, and ECHO) virus-like crystals have been seen in muscles of a single patient with ALS.

An investigator at Massachusetts General Hospital is studying the chronic demyelinative myelopathy induced in mice by intracerebral innoculation of tissue culture cell-adapted DA virus, using light and electron microscopy, with particular attention to changes in the anterior horn cells and peripheral nerves.

Motor end plates and peripheral motor nerve tissues from ALS patients are being studied for evidence of viral infection.

An investigator at the University of Southern California is studying the mechanism of ecotrophic wild mouse virus-induced neurodegenerative paralytic disease in mice. This approach includes studies on the model of replication of neurotropic type C virus in mouse neurons and determination of viral gene expression at the transcriptional and translational levels in neurons of paralyzed mice. The investigation focuses on the interaction of subvirion components with mouse neurons, which may alter or damage the neuronal membrane with consequent development of paralytic disease.

Ecotropic wild mouse type C virus-induced paralytic disease in mice is similar to several "slow virus" diseases of animals and man including human motor neuron diseases and spongiform encephalopathies. These studies on virus replication and gene expression in the central nervous system of paralyzed mice will provide insight into possible mechanism of neurodegeneration in parallel diseases of animals and man. These studies of in vivo passage and virus replication suggest that infection in the neonatal period may be an important step in induction of paralysis. The results also indicate that genetic recombination of replicating virus is not an essential parameter in the process of neurodegenerative paralytic disease.

Transmission of ALS to primates by inoculation of brain homogenates from ALS patients has failed. Isolation of virus failed after explanting, maintaining, co-cultivating, and fusing of non-neuronal CNS tissue from ALS patients. A comprehensive study was carried out on ALS patients in the Los Angeles area including serological evaluation for antibodies to mouse neurotropic C type virus, mouse leukemia agents, Gibbon ape leukemia virus, and endogenous type C virus of domestic cat. All were negative. Furthermore, examination of ALS tissue for the presence of antigens of mouse neurotropic C-type, electron microscopic examination of anterior horn cells, transmission of ALS tissue to mice, explantation of tissue into culture, and rescue techniques did not demonstrate mammalian type C virus in human ALS. A large number of the above described problems are being studied by a group at the University of Southern California.

Clinical studies at the "ALS Center" at St. Vincent's Hospital and Medical Center of New York of 98 ALS patients with quantiative muscle testing established slow, moderate, and fast stages. "Immediate" postmortem examination of 22 ALS patients, and 10 controls were performed. Histological and electron-microscopic studies confirmed the presence of giant swelling of proximal axons. Immunopathology showed immune complex deposits in astrocytes of the CNS. These cells functionally and mechanically support neurons and their injury or altered activity, possibly due to antibody, is of interest.

The immunological assessment of ALS patients showed that cell-mediated immunity to tuberculin was not depressed. Assay of blood T and B cell numbers and functional responses to standard antigens and stimulating substances were not different from controls. Lymphokine production (a measure of T cell function) in the presence of specific antigen such an tuberculin was not decreased. Humoral antibody (IgG, IgA, and IgM) levels and complement levels were similar to other neurological disease controls. Histocompatibility studies showed a decrease in incidence of HLA-9 antigen.

The possible association of poliomyelitis with ALS was also studied. Serum antibody response to poliomyelitis virus, however, paralleled that in the control populations. However, in vitro cell-mediated immunity to poliomyelitis virus was found to be greater in ALS than in other neurological disease controls, approaching that of vaccinated normals. The influence of polio vaccination on the incidence or course of ALS is not known at this time since the vaccination program began in the 1950s and vaccinated persons have not reached the age when this disease generally becomes manifest. The possibility that brain tissues of ALS patients becomes antigenic and causes development of autoimmunity to neuronal material was also studied. It was found that ALS patients had increased cell-mediated immunity to the isolates of ALS brain.

The viral isolation and co-cultivation studies of postmortem tissue and analysis of humoral antibody responses of ALS patients suggested a relationship between adeno-associated virus and ALS. This virus did not cause cytopathic changes when injected intracerebrally into neonatal mice. Antibody extracted from kidneys of ALS patients showed no viral specificity with known viruses except for 1 out of 9 ALS cases had antibody to poliovirus. Studies continue on parvo and picorna (polio) viruses with explant cultures and neurons isolated by gradient centrifugation.

At the "ALS - MS Center" at the Scripps Clinic and Research Foundation, several approaches are taken to achieve a better understanding of viral and immunopathogenesis of neurologic disease with the aim of learning the etiology and/or pathogenesis of multiple sclerosis, amyotrophic lateral sclerosis and other 'degenerative' diseases of the nervous system. These studies include work on viral persistence, immune modulation of viral antigens on the cell surface, killer and suppressor cells in experimental models and in man, and effects of persistent virus infection on differentiated cell functions. The studies employ a wide spectrum of modern immunological technology, some of which has been developed by these investigators.

CNS explant cultures were established. In the past year a search for Actinomycin-D resistant RNA was successful in 2 ALS cases. Search for adeno associated virus (AAV) was negative in 8 ALS cases; although antiserum response to AAV is increased, it is most likely an epiephenomenon. Purified neurons isolated from 5 ALS patients and 2 controls were analysed for polypeptide composition. No differences were noted. Five ALS and 2 control brain specimens were used to study aberrant gangliosides. Gangliosides are lipid materials present in membranes of neurons which act as receptors for various toxins, e.g. cholera toxin. An abnormal distribution of gangliosides was found in the sensory and motor areas of the frontal cortex of ALS patients. The nerve culture program confirmed neurocytoxic factors in ALS sera in culture of mouse spinal cord nerve cells. Similar serum factors were found in other neurological disease controls and individuals in contact with ALS patients. The serum factor was present in all stages of ALS.

Sera from 55 patients were analyzed for antineuronal cytotoxicity. Sera from ALS patients had increased toxicity, but did not correlate with ALS severity. The toxic factor is being characterized. Correlations of these laboratory investigations with clinical state and the stage of the disease by showing cause-effect relationships may have implications for specific therapy for this serious disease. Assay of patients T and B cell numbers and functional responses to PPD and ALS brain fractions were not different from the controls. No "immune" interferon was found in ALS patients sera and CSF suggesting that ALS is not an antimmune disease. Studies of Vesicular Stomatitis Virus pseudotypes in ALS explant cultures suggested the presence of an enveloped RNA agent or a cell type with an abnormal membrane and Actinomycin-D resistance.

The greatest hindrance to our understanding of the MND is the lack of suitable experimental models. Recently, the mutant Syrian hamster, showing hind leg paralysis discovered at Montefiore Hospital and Medical Center, is utilized in a study to assess its correspondence to certain human neuropathies, specifically ALS. The study has centered on the electron microscopic changes of peripheral axons and their coverings, the myelin sheaths. Several alterations have been observed. Mutant Syrian hamster with hind leg paralysis is used to study the pathomechanism of peripheral neuropathy. Changes in Schwann cells, accumulation of Hirano bodies, and associated filamentous accumulations and swellings in neurons were observed. These studies are done on young and old hamster mutants. The results confirm earlier findings that the Schwann cell membrane disappears at the region of filament accumulation and onion bulb formation. These studies are being continued in an effort to understand the relationship of the morphological changes to each other and to the symptoms they produce.

There are few models of neurotrophic virus-cell interaction, in large part because of the absence of neuronal cell lines in culture. One model of value has been the mouse neuroblastoma (NB) line, C-1300. Clonal sublines are available which are adrenergic and/or cholinergic. It is an established tumor line but can undergo morphological changes to a more differentiated behavior when treated appropriately: e.g., increased cAMP levels, serum deprivation, hypertonic treatment, or removal of a collagen substratum by treatment with collagenase. In addition to neurite appearance, there is often induction of neuronal enzymes and neurotransmitters. A cessation of cell division is characteristically also induced. Very little work has been done on the interaction of these cells with neurotrophic viruses although they are susceptible to rabies, hepatitis, lymphocytic choriomeningitis and herpes simplex viruses.

An investigator at University of Southern California proposes to develop "motor neuron degeneration" induced in NB cells by the cytopathic Theiler virus (TV) or its BHK-adapted, highly virulent subisolate designated DA. The TV and DA cause a neurodegenerative disease in mice and are related to the human picornavirus, polio. The investigators hope to gain some insights into the potential pathological mechanisms in amyotrophic lateral sclerosis.

PAIN

INTRODUCTION

Pain is the ultimate manifestation of some underlying etiological factors. Main causes of pain can be divided into two categories: one coming from without (heat, electricity, mechanical injuries, etc.) and the other from within (pathological and metabolic). Our primary goal is to alleviate this unpleasant sensation. This goal cannot be achieved realistically until we understand the causes that inflict pain. For example, if we can cure arthritis, there is then no pain because this disease exists no more. As such pain is neither a pathological or an environmental entity. Until we progress to that ideal stage, some realistic goals can be established and to achieve these goals, some practical approaches can be developed. The present state-of-the-science takes into account that no matter what underlying cause, pain is a real entity, and as such, needs remedial action.

All our behavior patterns have some basic cellular substrates where the stimulus is primarily received. By as yet unknown mechanisms sensory stimuli including pain are transmitted through cellular substrates to active sites from which all of our behavioral patterns emerge. Based upon this empirical assumption, the need then is to investigate the nature and the composition of primary site of impact. This, we will not understand until we know the normal makeup and functioning of the nerve cells. Thus as in any other scientific endeavor, understanding of normal functioning is prerequisite followed by the study of alterations brought about either by intrinsic disturbances or by external stimuli. Another objective is to understand how these impulses travel through the media and what changes are brought about by these impulses? What metabolites impede or accelerate the passage, and by what mechanisms can we alter these conditions.

The field of pain research and theory has developed rapidly in recent years. These developments have come from many disciplines, including psychology, physiology and clinical medicine. As a result of this progress, exciting new techniques have been proposed for the treatment of pain. The clinical syndromes which result from peripheral nerve injury bewilders the scientist who tries to understand them. Still worse, the failure to solve the problems they present means prolonged suffering and tragedy to many patients. People who face death due to a malignant disease such as cancer also face the prospect of extreme pain. Those who sustain brain damage as a result of a stroke may suffer severe pain for the rest of their lives. Drugs help, up to a point. Surgery offers some slight hope. But the pain may continue unabated until the end. Pain, then, is more than an intriguing puzzle. It is a terrible problem that faces all humanity and urgently demands a solution.

This report highlights the research supported by NINCDS as related to the six goals set by the pain panel of the National Research Strategy for Neurological and Communicative Disorders. Presently this Institute is supporting about 55 projects with an investment of more than three million dollars.

Identification of Pain Receptors and Characterization of their Physiological Properties

Most parts of the body or organs are supplied with one or more types of pain receptors. For example, most areas of skin contain more than one type of nociceptor. One type associated with myelinated fiber, responds to intense mechanical stimulation only. Another type is polymodal, which is associated with an unmyelinated fiber and excited by noxious stimulation such as heat, mechanical injury and chemical stimulation. A third type of nociceptors has been described as being associated with myelinated fibers and these respond to heat and mechanical injury. Both myelinated and unmyelinated receptors are found in muscle. Visceral pain is much less understood than skin and muscle pain. Since the viscera is well protected from the outside, the pain receptors in this region are probably activated by irritants produced by metabolic disturbances. So far, no definite pain receptors have been identified in the digestive tract.

The capacity to distinguish which primary sensory element contributes to a neuron's afferent input is a recent development. It is based on a decade of research establishing reasonably comprehensive surveys of the receptive characteristics for primary afferent fibers in nerves innervating a given body region. The considerable degree of selectivity in the responsiveness of different receptors and the relation of afferent fiber diameter to receptor type are points allowing the analyses of the projection from given receptor types. Electrophysiological recordings and the effects of lesions have been attributed to give types or classes of neurons on the basis of the source of activity. The recent evolution of an experimental technique allows a direct comparison, in the mammalian nervous system, of such structural features as connectivity for a particular neuron whose functional characteristics need to be established.

The sensitization of the C-fiber polymodal nociceptors can be related both to reactions associated with nociception and to the sensation of pain. For the latter, direct correlations have been made between activity in human C-fiber polymodal nociceptors and the report of pain by human subjects.

The functional significance of the substantia gelatinosa is known to be related to Lissauer's tract, which at various times has been implicated in the intraspinal transmission of impulses related to reactions typical of pain and to the manipulation of sensory information between segments or classes of receptors. It is quite clear from the clinical literature that injuries involving partial denervations or other interference with the afferent input to a spinal segment of the trigeminal input leads to essentially incurable dysesthesia, including various aberrations associated with pain. A great variety of both naturally occuring and artifical substances introduced excite or modify the behavior of these elements. For this reason, the work to date has been focused on attempts to use specific chemical agents to interfere with the evolution of background discharge. Since bradykinin is a prime candidate involved in the inflammatory reaction, as well as having been implicated in the process leading to skin pain, attempts were made to interfere with the bradykinin action by adding carbosypeptidase B to the perfusion fluid. Unfortunately, no definitive results were obtained in these studies. The results with an antiserotonin agent, methysergide alone or in combination with an antihistamine were more interesting. In particular, it was noted that the use of the antiserotonic agent tended to depress the development of background discharge following repeated heat stimulation. The effects upon the sensitization (enhanced responsiveness) were equivocal. Attempts to deplete serotonin by pretreatment with paracholorophenylalaine yielded results compatible with those obtained with methysergide.

Future trends: Polymodal receptors are prime candidates for forming part of the normal afferent system leading to the sensory experience. Significantly, they are known to be readily excitable by a variety of noxious stimuli, including, injected agents and irritant chemicals. A systematic survey would be made of the behavior of the polymodal nociceptors and other C-fiber receptors. A comparison of the behavior of each element to its own past activity, as well as comparison to other units studied, in the absence of stimulation, would serve as a guide for determining the possible influence of sympathetic stimulation upon this class of nociceptors. The work on the sensitization of nociceptors would be pursued with pharmacological agents or the efferent sympathetic stimulation. Similar work would be undertaken to identify and locate pain receptors in different organs of the body.

Pathways and Structures Modulating Pain

Of the several pathways contributing somatosensory information to rostral centers in man and lower primates, only the projection in the lateral and ventral columns of the spinal white matter has been established as crucial to nociception and pain sensation. In contrast to the paucity of evidence suggesting that dorsally-located tracts are essential for nociception and sensory pain, the evidence is overwhelming that fibers located in the ventrolateral white matter of the spinal cord are crucial to this function in normal individuals.

Classically, sensory pain and temperature sense are held to be affected in parallel by lesions of the ventrolateral spinal tracts; however, there appears no doubt that both natural and surgical interruption of parts of this system may cause a dissociation, leaving sensory pain relatively intact while interfering with temperature sensibility, or vise versa.

Regional or segmental modulatory influences on the effectiveness of nociceptor input have been suggested by studies in which dermatomal size and reactivity to stimulation has been shown to increase upon transection of nearby dorsal roots and/or Lessauer's tract. The observations, while not indicative of the locus of the modulatory effects, argue strongly for some form of regional interaction of nociceptive input, perhaps both tonic and evoked.

Data on electrical excitation of fibers in the ventrolateral tract provoking pain in man has been compared to similar data on fibers of antidromically excited cell bodies in monkey, as the basis of a contention that the "wide dynamic range" and multimodal cells of the deeper portion of the dorsal horn can provoke the experience of pain. This proposal assumes that the spinothalamic projections in man and monkey are quantitatively the same, as far as the size of the fibers and their respective characteristics, a point which is in doubt.

The trigeminal equivalent of the spinothalamic system is less well understood than is its spinal counterpart. The nucleus caudalis, particularly its more caudal spinal portion, is presumed to receive a major input from the nociceptive primary afferent fibers. The structure of the caudal part of the trigeminal nucleus is reminiscent of the more superficial portions of the dorsal horn; a marginal zone and substantia gelatinosa equivalent is underlaid by an apparent continuation of the nucleus proprius.

Nuclei of the reticular formation of the lower brainstem, such as the gigantocellularis and the ventralis reticularis, contain some neurons that exhibit nociceptive qualities and may be part of a nociceptive system, although at present evidence of their participation in mechanisms associated with sensory pain is lacking. A spinothalamic projection to the mesencephalic tegmentum has been demonstrated both morphologically and physiologically, and that part of this input reaching the periaqueductal gray matter surrounding the central canal has taken a special importance now that electrical stimulation in this region has been shown to exert potent effects upon various nociceptive reactions.

Three diencephalic regions receive significant projections from the spinothalamic pathways, and all three have been implicated in sensory pain. In primate, the principal somatosensory nucleus of the thalamus, the ventral posterior lateralis and ventral posterior medialis (ventrobasal complex), receive important input from the spinothalamic system that geographically overlaps the zones receiving a projection from the medial lemniscus. The spinothalamic distribution to the ventrobasal region differs morphologically from that of the medial lemniscus. Electrophysiological evidence of specific nociceptive neurons has been reported in ventrobasal complex. Recent morphological and electrophysiological studies have also emphasized another projection from the spinothalamic system to the medial thalamus. It reaches the vicinity of the centromedian and terminates in parts of the intralaminar group of nuclei (centralis lateralis and parafascicularis). Nociceptive responses by neurons in the intralaminar region and in what is called the centromedian (the exact limits given to this nucleus vary) have been reported in both animals and in man; they appear after a long latency, are related to activity in slowly-conducting myelinated and unmyelinated fibers, and fatigue readily.

It is believed that the cerebral cortex is not importantly involved in pain. Rarely, however, electrical stimulation of the cerebral cortex does apparently elicit reports of pain referred to the contralateral body. Several studies describe neurons in the primary somatosensory region, particularly Brodmann's area 3 and in somatosensory area II that respond to noxious stimulation in a selective fashion. Such neurons comprise only a small fraction of the population recorded from anesthetized or unanesthetized animals with intact ascending sensory systems, but become more numerous when the dorsal columns and dorsolateral tracts are sectioned. Whether the emergence of this population following interruption of the input to the medial lemniscus represents a behavioral change in these neurons or rather the uncovering of a population masked by other projections is not known. The region of the cortex critical for nociception (area 3) is known to receive an input from the ventrobasal nucleus of the thalamus and it in turn projects back to the same thalamic region as well as to other parts of the cortex. The peculiarity of small lesions producing a deficit of pain perception while large lesions do not, has been argued to reflect the interaction in the patterns of mutual excitation as well as inhibition of diencephalic structures and cortical areas.

Future trends: Knowledge of neural mechanisms of somatosensation is important not only because of its relevance to neural mechanisms of sensation in general but also because such knowledge will be important in the understanding of pain mechanisms. For example one of the thalamic nuclear group to be investigated is the intralaminar group. This nuclear group has long been implicated in sensation of pain because ablations in humans that include this region affect pain sensitivity and this region receives input not only from the classical pain pathways of the spinal cord but also from portions of the reticular formation and central gray that have also been shown to be involved in pain sensation. Any new information concerning the input to this region, therefore, will be relevant to the neural mechanisms of pain.

The theme of central modality segregation and electrophysiological characterization of quantitative properties in medullary and thalamic somatosensory neurons will be extended and amplified by anatomical studies of tracing projection neurons by using the method employing retrograde axonal transport of horseradish peroxidase. Electrophysiological mapping of specific mechanoreceptor representation in the thalamic ventrobasal complex will be performed in cats and monkeys using a chronic closed-skull preparation. Examples of each receptor category will be subjected to extensive quantitative study of input-output functions.

The effects of electrical stimulus applied to the body surface, to peripheral nerves and to the spinal cord on the perception of experimentally induced noxious stimuli will be determined. The neurophysiological studies will be directed toward determining: (1) the action of various descending systems on the responses of spinothalamic neurons to naturally evoked peripheral stimuli, and (2) the segmental mechanisms by which these effects are mediated. Emphasis will be placed upon the action of the systems arising in the brainstem.

Physiological, anatomical and clinical studies suggest two major ascending pain systems originating from fibers in the mammalian ventrolateral spinal cord: (1) a direct spinothalamic system projecting to the posterior (PO) and intraliminar thalamus and (2) a spino-reticulo-thalamic system projecting via the medullary nucleus gigantocellularis (NGC) to the centre median parafascicular (CM-Pf) thalamic complex. If each pathway is necessary for normal pain sensation, lesions selectively interfering with transmission along either of these pathways should reduce behavioral responses indicative of pain. Accordingly, quantitatively controlled noxious and innocuous thermal stimuli will be used in an operant escape paradigm to test the long-term effect of lesions within the NGC, PO and CM-Pf of cats and squirrel monkeys. Threshold-independent increases in escape latency will be used to detect motor deficits precluding normal responses. The functional selectivity and long-term electrophysiological effects of such lesions will be examined by periodic evoked potential recordings from electrodes chronically implanted within PO and CM-Pf. Comparison of the behavioral and electrophysiological effects of the lesions should permit identification of the ascending system(s) necessary and/or sufficient for pain.

An experimental subhuman primate model of central pain has been discovered. Macaques have been observed to predictably mutilate their hindlimb after undergoing a contralateral midthoracic anterolateral cordotomy of hemisection. Similar bizarre behavior has been observed in monkeys after total limb deafferentation. The same behavior occurred in one fortuitous case of a monkey with a pathological upper lumbar spinal syrinx. These phenomena suggest a remarkable parallel with the severe disturbing paresthesias in humans who had been subjected to the same neurological insult. The working hypothesis is that these phenomena result from interruption of transmission to and via the spinothalamic tract, which results in chronic abnormal discharge patterns at a diencephalic level. Various combinations of neurosurgery of spinal and peripheral levels have indicated that these paresthesias are largely independent of spinal mechanisms.

Brainstem mechanisms of trigeminal nociception are being investigated. The objective is to determine the relative involvement of each of four lower brainstem structures in the mediation of facial pain. These are: (1) the ventromedial border region of the trigeminal nucleus caudalis including the immediately subjacent lateral reticular formation, (2) the zona marginalis of the nucleus caudalis, (3) rostral medullary and pontine extensions of the lateral reticular formation and (4) the central core of the bulbar reticular formation. Two concurrent programs of research will be carried out. One will consist of acute electrophysiological experiments, principally with the cats, in which graded mechanical and electrical, noxious and innocuous stimuli will be applied to orofacial fields. Unit activity recorded extracellulary from responsive neurons in each of the four brainstem structures will be analyzed and guantified. Following histological verification to recording sites, data obtained from the four structures will be compared.

The other program will make use of two groups of waking unanesthetized monkeys with chronically implanted dental electrodes. Operant procedures will be used to obtain behavioral measures of pain induced by systematic, highly controlled stimulation of the tooth pulp through the electrodes. The measures will include escape thresholds and force of manual escape responses. Alterations in performance produced by discrete lesioning of the four brainstem structures will be studied in one of the groups of monkeys. Unit discharges evoked by pulp stimulation will be recorded from brainstem neurons of the other group of animals through indwelling, movable microelectrodes. Behavioral, anatomical and physiological data obtained from the two groups will be analyzed and compared. Ultimately the data will be used to provide a meaningful context for the interpretation of the results of acute electrophysiological experiments.

Endogenous Pharmacological Management of Pain

There are two main modes in pharmacological management of pain: exogenous and endogenous. The objective is to know what the endogenous substances are, how they are produced, where they are produced, what sensory system they affect and what their mechanisms of action are.

In the past decade, three major advances have been made in the area of pain research. First, neurons in the spinal cord dorsal horn involved in pain transmission have been identified. Second, brainstem sites have been discovered which produce profound analgesia when stimulated. Third, both opiate receptors and morphine-like peptides (endorphins) have been shown to be present in the vertebrate brain in areas that are important in analgesia production.

It has been shown that a neural substrate exists within the medial brainstem which serves normally to inhibit pain. This substrate may be activated by electrical stimulation or by morphine. Speculatively, it may be suggested that morphine acts directly at opiate receptor sites whereas electrical stimulation may, at least in part, act upon these sites indirectly via the release of the endogenous, morphine-like substance. The rationale for undertaking this kind of investigation is to develop modes of activation of this endogenous analgesic process without exogenously administering pharmacological agents. These developments evidently will lead to a better understanding of the nature of pain and may have a potential benefit in pain control.

There is now considerable evidence indicating that activity of neurons in discrete brainstem regions can strongly inhibit pain transmission. The first indication of this was the demonstration that electrical stimulation through electrodes implanted in the dorsal raphe nucleus and the mesencephalic periaqueductal gray in rats produces profound analgesia. Subsequent studies have demonstrated that analgesia can be produced in cats, subhuman primates, and man by stimulation of analogous brain sites.

Recent pharmacological studies are beginning to clarify the mechanism of opiate analgesia. Substances have been found in mammalian brains which bind morphine and other opiate drugs stereospecifically and in rough proportion to their analgesic potency. In addition to this opiate receptor, compounds which show high and stereospecific binding to opiate receptor have been isolated from mammalian brain and subsequently identified and synthesized. These compounds, called enkephalins, are pentapeptides which have the pharmacological properties of opiate agonists. Enkephalins produce only brief analgesia unless structurally modified to prevent rapid degradation, or injection directly into the midbrain. Both enkephalin, and the opiate receptors are concentrated in discrete regions of the brain which overlap extensively. Moderately high concentrations of enkephalin and opiate receptors, are found in periventricular thalamus and mesencephalic periaqueductal grey, which are effective sites for electrical stimulus-produced analgesia (SPA). Also, when small amounts of opiates are injected into these regions, analgesia is produced. The overlap in mesencephalon and diencephalon of sites for SPA or opiate analgesia with regions of high concentration of opiate receptors and enkephalin has raised the possibility that narcotics and electrical stimulation produce analgesia by a common mechanism, i.e., activation of an endogenous brainstem system. This system may operate under normal physiological conditions to suppress pain and is mediated by a descending control system arising in the brainstem which inhibits pain transmission neurons in spinal dorsal horn and trigeminal nucleus caudalis.

Opiate receptors: It has recently been established that there are opiate receptors in the vertebrate central nervous system. The presence of receptors has taken on even greater significance with the discovery of the endogenous brain ligands for it. Although the anatomical distribution of the opiate receptors varies in different species, there are many common elements. In most species the highest concentrations of opiate receptor are found in the striatum. In monkeys and humans, however, the limbic structures contain the highest levels with moderate levels in the striatum. All species studies have shown moderately high levels of receptors in the midbrain, especially the periaqueductal gray. Cortical levels are consistently low. Endorphins are found in multiple forms in the brain, e.g., leucine and methionine enkephalin and the pituitary hormone beta-endorphine, is a potent analgesic and strongly binds to the opiate receptors. In fact met-enkephalin is identical to part of the beta-endorphin molecule. Nevertheless, there is considerable overlap in the distribution of the enkephalin and opiate receptors. For example, in the rabbit, rat, and monkey, the highest levels of enkephalin are found in the striatum. Moderate levels are found in the midbrain and low levels in the cerebral cortex.

In summary, the areas of the brain where opiate peptides are produced or located and their anatomical distribution have been identified. Pain pathways specifically being affected have been worked out. Chemical characterization and their pharmacological implications seem to be underway, and opiate peptides-induced analgesia by electrical stimulation has shown analgesic action similar to that which is produced by morphine.

Future trends: During the past few years, at least 12 separate peptide substances have been structurally identified and shown to be present in significant quantities in the brain. Almost without exception, the highest concentrations of these peptides is in the hypothalamus, with particularly high concentrations in the neurovascular zone of the median eminence. Several of these peptides have clear functions in relation to anterior pituitary control; others, although shown in influence hormonal secretion, may function primarily in other regions of the brain related to sensory conduction, pain mechanisms, and behavioral responses. Receptors for many of these substances are now being searched for in brain tissues and pathways linking peptidergic systems are currently under investigation using neuroanatomical tracing techniques and immunocytochemistry. To achieve these objectives, research is being carried out with detailed analyses of: The neuroanatomy of peptidergic pathways, the neurophysiologic effects of peptides and a definition of their sites of action, neuropharmacological studies to identify receptor sites on neural tissue and to identify agonists and antagonists that might have therapeutic implications, analysis of the hormonal and cerebrospinal fluid distribution and effects of peptides as well as the analysis of the behavioral effects produced by these substances.

Some of the aims directly or indirectly related to peptide analgesia with similar functional aspects will be emphasized; these include, the investigation of spinal cord mechanisms of stimulation-produced analgesia to learn more about the descending paths from analgesia-producing areas of the medial brainstem to the spinal cord sites of sensory inhibition. Also in this series of the experiments, the nature and locus of the inhibitory mechanism in the cord will be examined.

The interrelationship between normal biological states such as fear and the operation of the brainstem analgesia system will be investigated. There are two different major objectives to these studies: (1) To learn whether or not the analgesia system, in addition to blocking sensory transmission of nociceptive origin, also directly inhibits higher affective states such as fear which are associated with pain perception; and (2) That the pain inhibitory system lying within the medial brainstem is a normal, endogenous one, to ask the question of how biological states such as fear might affect the normal operation of this system. That is, if pain inhibition is the normal function of this system, what are the normal physiological accesses to this system which turn it on or off?

Further investigations are directed toward elucidating the role of the raphe nuclei in mechanisms of nociception and anti-nociception as well as the possible modulatory influence of other, monoamine-containing cell groups on the analgesia system.

Brain areas will be explored from which the analgesic effects of electrical stimulation are elicited and are not reversed by naloxone. It is likely that two different kinds of analgesic systems coexist in the medial brainstem, one which shares properties in common with morphine or an endogenous, morphine-like substance and hence is sensitive to naloxone and other which does not.

The phenomenon of morphine-mania will be investigated with microinjections of the drug into discrete brain regions, in the hope of learning something of general interest about morphine's mode of action by studying the peculiar response to this substance.

Recently, two synthesized morphinomimetic penta-peptides (methionine-enkephalin and leucine-enkephalin) have been synthesized. These will be tested in normal brain tissue by microinjecting these substances into discrete regions of the rat brain.

Experimental and Therapeutic Techniques

Transcutaneous electrical stimulation: The importance of descending pathways in modifying the processing of sensory input is well known. Emphasis has been placed upon those interactions which occur at the spinal cord level. Interactions of this type have been specifically implicated in modifying the central action of noxious stimuli.

Since many of the descending pathways mediating these effects are also activated in the generation of motor behavior, it is likely that the resulting performances of motor tasks may affect the information processing of spinal inputs activated by both noxious and nonnoxious stimuli. These studies will provide insight into the degree to which motor behavior can modify the perception of noxious and nonnoxious stimuli which could be an index concerning the nature of perceptual changes induced in chronic pain patients. This procedure using externally applied stimuli could be employed in evaluation of therapeutic devices as well as for drug efficacy. For example, it will be worth examining the interaction of aspirin and transcutaneous electrical nerve stimulation with respect to their additive or supperadditive effects on the response of normal subjects to experimental noxious and nonnoxious thermal stimuli.

The evidence of interaction of salicylates (aspirin) and transcutaneus electrical nerve stimulation (TENS) is mediated by the endgenous opiate system, since it is reversed by narcotic antagonists such as naloxone. It is possible that TENS may produce analgesia indirectly by mobilizing the release of endorphins (precursors of endogenous opiates) in the spinal cord and that these in turn bind to opiate receptors. It has been found that, in patients with chronic pain, TENS elevated the level of endorphins in the cerebrospinal fluid drawn from the part of the cord which received inputs from the region of the body to which the TENS was applied, whereas the level of endorphins in more distant parts of the cord remained unchanged. It has also been observed that a mixture of codeine and aspirin given orally produces a superadditive analgesic effect. These observations suggest that aspirin and TENS together might produce a higher level of analgesia than is possible with either alone. Therefore, a study is being conducted to determine if in fact the effects of aspirin and TENS are additive or superadditive and, if so, how this type of phenomenon is reflected in changes in variables assessed.

Use of Noxious and Nonnoxious Stimuli: The effects of the chronic pain state on the perception of thermal noxious and nonnoxious stimuli need to be determined to know whether a modification in the processing of sensory information has occurred in individuals who have suffered from a chronic pain state. These patients are to be compared with the responses of patients with temperomandibular joint pain syndrome and tic douloureux in order to assess the extent to which chronic pain may modify both the discrimination of noxious and nonnoxious thermal stimuli. The rationale for this type of research would be to provide quantitative evidence that the clinical condition of chronic pain does in fact modify the CNS in such a way that the perception of acutely applied noxious and nonnoxious stimuli is altered. This would further emphasize the importance of treatment programs designed not only to modify the behavior of chronic patients but also to treat the source of the chronic pain itself.

The experiments on the effects of chronic pain state on the perception of thermal nonnoxious and noxious stimuli are designed to examine long-term modifications of information processing in ascending sensory systems which may result from chronic pain. Given the potential of the central nervous system for localized trophic phenomena, it would not be surprising that a protracted chronic pain could be associated with long-term modifications in the activity of central pathways, which in turn might affect the perception of acute noxious and nonnoxious stimuli. Some evidence in the literature suggests that modifications of this type may in fact occur. Using a pressure algometer, it has been demonstrated that patients with substantiated organic basis for their pain had elevated thresholds to noxious stimuli applied with the algometer. Using a variety of noxious stimuli, including the pin prick, pressure algometry, and electric shock, it has been shown that hypochondiracs were extremely reactive to noxious stimuli, having a greater reactivity than normal subjects. However, the reactions of patients with organic pain varied depending upon their psychological state. For example, depressed patients with pain had elevated pain thresholds, while anxious patients with pain had decreased thresholds. Earlier work showed that the threshold for experimentally applied noxious stimuli decreased following relief of root pain in paraplegics, suggesting that modifications in perception can occur, not only when chronic pain is present, but also after it has been successfully treated.

Use of Implantable Stimulating Devices: It is also important to determine the effect of electrical stimuli applied with implantable stimulating devices to peripheral nerves and to the dorsal and ventral surfaces of the spinal cord on the perception of noxious and nonnoxious thermal stimuli. Because of the tremendous social and personal cost from causes of chronic pain, it is imperative that many possible therapeutic modes be assessed by which analgesia may be produced. Although there is currently a considerable lack of enthusiasm for the use of electrical stimulation techniques to modify pain perception, it is the consequence of inadequate evaluation of these devices using sound scientific methods. These psychopysical experiments can provide a strong data base for assessing precise features of pain perception. Because of the sensitivity of these measurements, their use could lead to employment in studies of appropriate stimulus parameters and stimulation sites to optimize the effectiveness of this technique in the management of clinical pain. They may even provide guidelines for the evaluation and subsequent utilization for producing analgesia in the CNS stimulation for producing analgesia.

The use of implantable stimulating devices for producing localized analgesia has been attempted systematically since the gate theory was proposed. Despite the remarkable usefulness for this approach to treating chronic pain, very little has been done to quantitate the effects produced by these devices. Some of the preliminary data suggest that, under certain conditions and in certain patients, these implantable devices may produce marked therapeutic effects. However, further development of these devices requires more detailed information regarding the precise way in which they modify pain perception. In addition, factors pertaining to patient selection and the nature of pain problems treated by this technique may be much more objectively addressed if the relevant psychophysical data were available concerning the manner in which these devices actually affect the perception of noxious stimuli.

Current activities are directed toward determining if the perception of experimentally induced noxious and nonnoxious stimuli, as characterized by the measurement of discriminability using signal detection theory, can significantly alter pain perception. This approach discriminates psychological bases of pain from those of physiological origin. Using this technique, effects of electrical and thermal stimulation on chronic pain patients are being evaluated, such as effects of motor behavior on the perception of thermal noxious and nonnoxious stimuli, interaction of transcutaneous nerve stimulation and aspirin, effects of the chronic pain state on the perception of thermal noxious and nonnoxious stimuli, and the effects of electrical stimulation applied with therapeutic devices on the perception of noxious and nonnoxious thermal stimuli.

Future directions involve investigation of safe and effective means of applying external stimuli and develop means of delivery of stimulus not only at the external surface of the body but in deeper specific regions of the CNS. Electric stimulation techniques seem to be superior to other procedures. They apparently are nondestructive of brain tissue and can be used repeatedly as the need arises. Other analgesic agents need to be developed to augment the therapeutic efficacy of the stimulation technique.

Surgical Control of Pain

Surgical procedures, especially on the CNS are considered a last resort when physical, pharmacological and even psychological procedures prove to be ineffective. Our current knowledge regarding regeneration and plasticity of nerve fibers is inadequate; once they are severed, they do not regenerate. For this reason, surgical procedures for relief of pain are performed only on terminal patients, such as those with cancer, or a situation where either sensory or motor function is not affected. In non-terminal patients, such surgical operations have also proved ineffective since pain sensation generally returns after six months to a year after such operations. The rationale for conducting these studies is to know why pain returns and what mechanisms are involved in these situations. Elucidation of these mechanisms would help a sizable proportion of the population including those who suffer from chronic pain, chronic low back pain, pain caused by a herniated disc, and pain caused by fibrous thickening, etc.

Recovery of pain reactivity following sequential lesions to the spinothalamic tract and other cord sectors of monkeys indicates that although the lateral spinothalamic tract of primates has been considered classically as the major pathway for ascending spinal conduction of pain, it has been known for some time that chronic pain sensation returns following chordotomy in humans. Recent physiological analyses of those spinal pathways receiving input from peripheral nociceptor elements has led to suggestions that each of the following pathways could participate critically in the recovery of pain sensitivity following chordotomy: the dorsal columns, Lissauer's tract, the spinocervicothalamic tract, the ventral spinothalamic tract, and the spinoreticular tract. To test these possibilities, unilateral chordotomies were performed on monkeys. Following recovery from contralateral analgesia, the other cord sectors were lesioned. The most pronounced deficits were observed when the chordotomy sectioned the entire ventral quadrant. The lesions that produced the most enduring secondary pain deficit was ventral hemisection. In contrast, a variety of dorsally placed lesions produced either no secondary dimunution of pain sensitivity or a transient effect. Clinically, surgical procedures have in some instances provided pain relief by spinothalamic cordotomy. A number of cancer patients have been helped by hypophysectomy by removal of the pituitary gland. Similarly, lesions placed in some areas of the upper brainstem have provided relief which in some instances lasts for several years.

Current activities include investigation of spinal somesthetic pathways of synaptic circuitry in the dorsal horn and other neurons, e.g., gelatinosa, nucleus magnocellularis; investigations of the source of those boutons which end on marginal neurons but do not degenerate following either multiple dorsal rhizotomies or Lissauer tractotomies; resolution of the issue of the level at which the spino-reticular relay takes place (medulla vs. mesencephalon) because this has major implications for the understanding of the nociceptive pathways both for the future experimentation and for the possible placement of chronic stimulating electrodes for control of pain in man.

Future emphasis is placed on investigation of pathways, neurotransmitters or other CNS mechanisms that can be surgically manipulated to control pain; search for clues to the involvement of hormones and hormonal glands, e.g., pituitary gland, in the control of pain; development of new microsurgical techniques and the improvement of the existing ones.

Pain Evaluation

There are at present several methods used in the evaluation of pain perception. Most of these techniques employ external stimuli such as heat, pressure or electrical impulses. These manipulations result in behavioral manifestations generally referred to as escape mechanisms of reflex actions. The degree of escape is then either measured by mechanical means or by physical displacement of limbs, such as tail-flicking, jaw-opening, reflex evoked by tooth pulp stimulation, avoidance behaviors in hot place test, paw-lick, flinch, jump, vocalizations, etc. In human studies there is an additional advantage or disadvantage in that the pain experiences elicited by physical means cannot be objectively evaluated. These experiences are invariably influenced by the psychological state of the person involved. On the other hand, the advantage is that the responses to the experience can be communicated verbally. The rationale for pursuing these studies is to devise sound and reliable methods by which response to any stimulus or analgesic agents can be evaluated objectively without being influenced by human emotions.

Current State of Knowledge: One of the most difficult problems facing the experimenter who wishes to study the psychophysics of pain perception is determining the method by which the stimulus is to be reported by the subject. In order to objectify the responses to noxious stimuli, some investigators have assessed the autonomic responses which are evoked. However, changes in physiological parameters may be uncorrelated with the subject's verbal assessment of the noxious stimulus. Moreover, certain physiological indicators which have been employed, such as grimacing, are likely to be at least as variable as verbal reports by the subject. The use of autonomic changes has the additional drawback of reflecting activity in specific reflex pathways which may not be related to alterations in supratentorial interactions which are felt to play a role in nociception. Therefore, if only these responses are measured, some important differences between the moderate stoic and the moderate hysteric might not be discernable.

Although it has been argued that the use of verbal reports may be extremely unreliable, these reports may provide the most important and hence most valuable source of information about the pain experience. The use of a dolorimeter suitable for applying quantitative thermal stimuli made it possible to use the verbal report of a subject in response to measurable amounts of thermal energy applied to the skin surface as the basis for developing as basis for developing a quantitative psychophysical assessment of pain perception. Although it was possible to demonstrate that the dol scale had a firm psychophysical basis and correlated with other measurement of pain perception, the use of this method for quantifying the verbal response of the subject has not been widely used. In addition to the experiments examing responses over an entire intensity continuum, attempts were made to evaluate Pain thresholds using a method of limits or a constantly increasing or decreasing stimulus. To reduce the variability that commonly occurs when using these techniques for evaluating pain perceptions and its alteration due to the action of analgesic agents, pain tolerance tests were developed. Studies assessing the analgesic action of morphine and morphine derivatives emphasized the value of using pain tolerance under some conditions, in addition to the traditional pain threshold measurements. Variations of these techniques such as the use of the cold pressor pain have also been employed.

Although the use of these methods has yielded very valuable information, certain inadequacies became apparent. These inadequacies related principally to the difficulty in utilizing these measurements to gain an understanding of the psychophysical processes involved in nociception rather than an inadequacy in demonstrating changes *per se* in the response to pain by various therapeutic and experimental procedures. First the variability in the absolute measurements of pain thresholds among subjects was considerable. The second and perhaps major limitation of the methods employing the assessment of pain tolerance and pain threshold is that the complex psychophysical process underlying nociception is represented by only one measurement. It is generally agreed that the report of pain is a function not only of the actual sensory experience, but also of the subject's tendency to bias his description of what he perceives. In a study of nociception, it would therefore be desirable to have means of assessing both of these factors. One attempt to assess the sensory component of the pain experience, independent of response bias, has involved the use of signal detection theory. As it is applied to psychophysical studied, two independent variables can be calculated from the data base. The first, usually referred to as discriminability which is a measure of the subject's tendency to distinguish between two different stimuli. The second variable is the likelihood ratio or criterion, which reflects the "rules" by which the subject assigns a certain description to a given sensation. Because signal detection theory has proven to be useful in other psychophysical paradigms as a means of dissociating changes in the cognitive and sensory components of a response into change in criterion and discriminability respectively, several investigators have attempted to adapt this method to the study of nociception and analgesia.

Other compounding factors: Application of signal detection theory to the assessment of pain and evaluation of analgesic drugs has been criticized from several points of view. However, in the absence of any available method by which one can realistically evaluate magnitudes of pain unrelated to psychological influence, this theory comes closest where apparent bias may be ruled out. Several studies have been conducted which show that the difficulty lies not only in the assessment of true pain experience alone, but pain experience can also be altered by environmental factors such as physical distraction, sound, etc. This further compounds the problem of pain assessment. Some of the compounding factors are given below. The importance of suggestion has been emphasized in modifying certain aspects of sensory perception. In studies of nociception, the effects of suggestion, particularly placebo effects have been considered. Most of these studies are directed toward determining the analgesic effect of suggesting to the subject that a device, drug or type of manipulation may actually produce a modification in pain perception. Many studies have shown that, if the patient believes that a certain procedure or compound will modify his sensory experience, a modification will indeed occur. However, the data also suggest that the specific perceptual changes induced by the placebo may be different from those produced by the actual substance or procedure. Moreover, the effects of suggestion on the specific quantitative changes in the variables assessed using a signal detection theory analysis can be different, depending on the type of suggestion and the paradigm in which it is employed.

The problem of suggestion was examined from a different perspective. Rather than suggesting verbally to the subject the direction of a probable analgesic effect, sham electrical stimulation was applied using neutral instructions. Under these conditions, the "suggestion" that electrical stimulation was actually being applied resulted in a change in discriminability rather than in criterion. Together, the results from all of these studies imply that the effect of suggestion is dependent upon the nature of the suggestion Per se as well as the paradigm in which it is employed.

Studies have demonstrated that hypnosis also affects pain perception. Several speculations have been made concerning the mechanism by which this effect is mediated. The studies demonstrated that the analgesia produced by hypnosis is very likely unrelated to the mechanism by which a placebo produces analgesia. In fact, it was demonstrated that subjects who were very easily hypnotized had a much more marked analgesia and smaller placebo effect than those who were more difficult to hypnotize. The "analgesia" produced by the placebo, however, was comparable to that occurring mechanism of hypnosis but is not related to either a placebo effect or to the fact that there may be a reduction in anxiety associated with hypnosis. Rather it is attributed to the analgesic effect to a transient amnesia or disorientation phenomenon produced by this procedure. It is shown that a marked analgesia to cold pressor pain could be produced by hypnosis under conditions in which the subject was capable of objectively reporting the intensity of this stimulus. The fact that mechanisms underlying the analgesia produced by hypnosis are, in fact, due to mechanisms other than those related to the action of morphine is supported by the finding that hypnotic analgesia effects were not reversed by naloxone.

Anxiety has also been shown to produce an alteration in nociception. In the very early studies the presence of anxiety induced by the stimulus paradigm was found to be associated with an increase in the reaction to noxious stimuli. The effect of anxiety may in part be due to the resulting distraction. The effect of distraction produced by three techniques was examined: a story, an additional task, and a counting task. It was found that if the story or the additional task were presented throughout a two minute period of painful stimulation, a reduction in the report of pain and a reduction in the percent time that the subjects reported attending to the pain was observed. The fact that distraction may also decrease at least the awareness of clinical pain has also been emphasized. It has been shown that auditory stimulation, particularly when accompanied by suggestion, produced alterations in pain perception. For example, the application of auditory stimuli produced an elevation in the amount of electrical stimulation that had to be applied on the dorsal surface of the forearm in order to evoke a report of pain. The effect of distraction was produced not only by sensory stimuli, but sensorimotor tasks as well. It was found that the phantom limb pain was reduced by the use of sensorimotor tasks as well as by nonnoxious sensory stimuli when applied repeatedly throughout the rehabilitation of the patient.

This program supports investigations of a variety of slow or persistent viruses and viral infections. The research is relevant to the elucidation of the etiology and/or pathogenesis of multiple sclerosis, amyotrophic lateral sclerosis, and probably other degenerative neurological conditions. some of which may be associated with aging.

As of July 2, 1980, 31 grants were active in the infectious diseases subprogram. Total costs for these research activities is $ 2,295,489. A total of 30 applications were received. Twenty-six were approved, of which 4 new and 3 competing renewals were funded at a total cost of $ 189,754 for new research grants and $ 276,415 for competing renewal grants.

A variety of disorders involving the central nervous system (CNS) have no known cause. Many of these may be the result of virus infections. It is suspected that these disorders may arise from what is termed a "slow virus" infection. In this case, the actual virus infection may have occurred years before the disease actually manifests itself. It is likely that not all people infected with the virus actually develop disease. It is also likely that a variety of factors can stimulate an infected person to develop the disease. These characteristics make it difficult to pinpoint a single event as a cause of the disease and dictates that a multidisciplinary approach must be used in order to accurately identify the cause or causes of disease. It is thus of interest to examine diseased as well as normal tissues for the presence of specific viruses.

To do this very sensitive methods for detecting the presence of a specific virus must be utilized. It is not known how many CNS cells need to be infected with virus to produce a diseased state. It is likely that a small fraction of cells in a crucial area could disrupt neural function. One virus particle can easily be detected only after it grows and multiplies into many viruses. The inability to recover a growing virus from a tissue does not mean, however, that a virus is not present in the tissue. A virus may be able to perpetuate itself in cells but be inherently defective in its ability to produce an infective virion. This virus may, alternatively, be perfectly capable of forming large numbers of highly infectious virus progeny. It may be in a latent state, however, and need a particular stimulus to initiate multiplication. Unless the appropriate stimulus is used, this virus would remain undetected by the growth assay. Another virus might be particularly labile and be inactivated by remaining in dead tissue for even a short time. Obviously, the virus detection method used for these studies must be highly sensitive, specific and flexible in its ability to detect the presence of virus no matter what form or state of activity it is in.

One portion of the virus, the viral nucleic acid, must be in the tissue if the virus is present at all. Consequently, nucleic acid hybridization provides a highly specific, extremely sensitive means for uncovering the presence of defective or competent viral nucleic acids, even when there are no viral gene products or infectious viruses present in the tissue.

An investigator at Harvard studies cell tropism of reovirus, and uses this virus also as a probe for cell receptors. The hemagglutinin of reovirus, encoded in the S1 gene, is responsible for the central nervous system cell tropism of reovirus types 1 and 3. This has been shown utilizing viral recombinant clones which contain nine genes of one serotype (type 1 or 3) and the S1 gene from the other type. Clone 1.HA3 contains nine genes from type 1 and the hemagglutinin from type 3. Clone 3.HA1 contains nine genes from type 3 and the hemagglutinin from type 1. Reovirus type 3 and recombinant clone 1.HA3 both produce a fatal encephalitis in newborn mice which is associated with neuronal destruction but causes no damage to ependymal cells. Reovirus type 1 and recombinant clone 3.HA1 produce a nonfatal infection of ependymal cells with no effect on neurons. Immunofluorescent studies have demonstrated that there is no production of viral antigen in ependymal cells of animals infected with reovirus type 3 or clone 1.HA3 and no production of viral antigen in neuronal cells of animals infected with reovirus type 1 or clone 3.HA1. In addition, the patterns of viral growth in the central nervous system of infected animals is linked in an absolute way to the viral hemagglutinin. Maximal viral titers of 10^{10} plaque forming units (pfu) occur in brains of animals infected with reovirus type 3 or a variety of recombinant clones that contain the type 3 hemagglutinin. Maximal titers of 10^8 pfu occur in brains of animals infected with reovirus type 1 or recombinant clones which contain the type 1 hemagglutinin. These studies have demonstrated that the pattern of central nervous virulence, cell tropism and viral replication of reovirus is determined by the S1 gene and probably relates to the specific interaction of the viral hemagglutinin with receptors on the surface of either ependymal cells or neuronal cells.

Using reovirus as a probe for cell surface receptors, they have found that reovirus type 3 binds to murine and human lymphocytes while reovirus type 1 does not bind to murine lymphocyte and binds minimally to human lymphocytes. By analyzing the binding characteristics of recombinant clones containing genes from both reovirus types 1 and 3, they were able to determine that the S1 gene, the gene that encoded the viral hemagglutinin, is responsible for the binding properties of reovirus to lymphocytes. The binding assay used involves incubating lymphocytes with purified viral particles, labeling attached virus with FITC-labeled antiviral antibody and analyzing binding characteristics on a fluorescence-activated cell sorter. The binding sites for the viral hemagglutinin are present on a subpopulation of both T and B lymphocytes and appear to be present on a greater percentage of B than T cells. The virus is not binding to the lymphocyte surface via structures encoded for by the major histocompatibility complex as they were unable to block binding with anti-H-2 antiserum. Moreover, binding occurred to a cell devoid of histocompatibility antigens. Since *in vivo* cell tropism of reovirus type 3 for neuronal cells in the central nervous system is also determined by the viral hemagglutinin, it is possible that the binding properties of the viral hemagglutinin have identified a surface structure shared between neurons and lymphocytes.

In order to detect viruses as sensitively as possible, an investigator at La Jolla Cancer Research Foundation has: (a) developed methods to produce various radioactive viral nucleic acids to be used as probes to specifically detect the presence of certain viruses in the CNS tissue; (b) modified nucleic acid hybridization methods in order to increase the sensitivity of virus detection; (c) made basic discoveries in the area of nucleic acid hybridization which should allow an increase of the sensitivity of viral detection by 100-1000 times. The modified test currently used will specifically detect the presence of one copy of virus RNA per 300 cells when one gram of tissue is used in the assay. The best radioimmune assays will detect about 10-15 moles of antigen while the hybridization method will detect the presence of 10-18 moles of virus RNA. These methods will be used to examine multiple sclerosis, amyotrophic lateral sclerosis and Parkinson's disease tissue for the presence of measles, polio and influenza viruses. These viruses have been implicated in these diseases.

Following the development in recent years of the concept of "slow" and "latent" virus infections and the discovery that Kuru and Creutzfeldt-Jakob disease are caused by transmissible agents, there has been a flurry of activity in the search for the possible viral etiology of multiple sclerosis and other "degenerative CNS disorders. Viruses in the herpes group have been found to be "latent" in nervous and other tissues of asymptomatic individuals. The varicella-zoster virus may be "latent" in dorsal root ganglia of the spinal cord and its reactivation leads to clinical herpes zoster. Human cytomegalovirus may remain latent and be activated by immunosuppression in renal transplant patients. Epstein-Barr (EB) herpesvirus may be "latent" in lymphocytes of individuals who have had infectious mononucleosis. Latent infectious herpes simplex virus (HSV), has been isolated from the trigeminal and dorsal root ganglia of humans and experimental animals. In one study "latent" HSV infection of the trigenimal ganglion was found in 50 percent of unselected individuals at autopsy.

It is possible that with present techniques "latent" virus cannot be isolated or identified if there is only a small amount of complete virus present.

Experiments in recent years using nucleic acid hybridization and renaturation kinetics have been undertaken to determine the presence of viral nucleic acids in transformed and neoplastic cells.

An investigator at the University of Wisconsin is studying the morphology of chronic viral infections of the brain. The overall objective of the research is to collect data concerning a human papovavirus (JCV) first isolated at that University in 1971, which was derived from a human brain with multifocal leucoencephalopathy. The virus employed in the animal experiments is one of two new human papovaviruses of the polyoma subgroup which have a world-wide distribution and which infect mostly persons early in life without causing any distinguishable illness. The studies focus on the tumor-inducing capability of this virus, in order to develop models of human neoplasms, particularly of the nervous system. The development of medulloblastomas in Syrian hamsters is of especial interest since this is a model for a highly malignant brain tumor in children. Primary malignant brain tumors were induced in three owl monkeys. The papovirus is the only human virus which can induce solid tumors in a subhuman primate. In addition to solid tumors, 2 monkeys displayed a more diffuse neoplastic condition of the brain which also displayed a more diffuse neoplastic condition of the brain which also has a counterpart in man where it may occur as a sporadic familial disease. The potent oncogenicity of JC virus has stimulated a worldwide search for genetic evidence of polyoma-virus infection in human brain tumors by recently developed techniques of molecular biology. Several papers have claimed positive evidence for such infection in meningiomas and glial tumors.

The major objective of a research project at Yale University is to study the pathogenesis of experimental Creutzfeldt-Jakob disease (C.J.D.) in laboratory animals, like guinea pigs, hamsters and mice. Selective light microscope, electron microscopic (E.M.), virological, tissue culture and biochemical techniques are utilized. The leading hypothesis is that the C.J. agent is composed of various strains with distinct incubation periods which cause lesions having characteristic distributions. The second hypothesis is that C.J. agent is a variant of the scrapie agent.

Cells from C.J. infected brains established permanent long term tissue culture lines, which died out after 50 passages in vitro. Furthermore, tissue culture cells arising from C.J.D. brains were capable of occasional growth on soft agar, unlike normal brain cells which formed no colonies. The attempts, however, to produce tumors with the C.J.D. tissue culture cells by injecting them subcutaneously into immunosuppressed animals and nude mice failed.

The role of scrapie virus in aging and other conditions, is being studied by an investigator at New York State Department of Health by the neonatal inoculation of mice with scrapie virus intraperitoneally. The results may shed light on human presenile dementia and may have implications in the spongiform encephalopathies. They have discovered a complex interaction between concurrent infection in the same animal with lymphocytic choriomeningitis (LCM) and scrapie. LCM super-infection of mice which were also infected with scrapie, was proposed as one means of interacting (with LCM as a probe) with the lymphocyte T cell system during early build-up of scrapie spleen titer following IP inoculation. It was predicted that by causing a rapid turnover of T cells, the LCM infections might cause the death of many scrapie infected foci, if these were, as postulated, in T cells or in T cell precursors. They hypothesized that superinfection with non-lethal LCM should lengthen the incubation period of IP scrapie. This prediction has proved true. Not only is the incubation period lengthened, but some mice are apparently spared from scrapie death by the intercurrent LCM superinfection. This effect is time dependent in terms of the interval between the scrapie and LCM inoculations.

A further, unexpected effect, is that in a certain range of the scrapie/LCM time interval, an opposite effect occurs, whereby the scrapie incubation period is shortened to the point where intraperitoneal (IP) inoculation gives a shorter incubation period which compares closely with that expected from a intracranial (IC) inoculation. Thus, they have tenative, though unconfirmed, data which suggest that an LCM infection of the brain, occurring during an early period of scrapie IP incubation, can convert the infection to an IC one, with early fatal results. They believe that there are to postulate that this phenomenon may occur in human C.H. disease. Further, it is conceivable that human C.J. only occurs if an otherwise harmless visceral infection is converted to an IC one, by an intercurrent mild viral (or other) encephalitis. This concept may be operative in the explanation of the mystery of C.J. infective origin in man, plus the low incidence of overt disease. By the same token, the phenomenon may be relevant to Alzheimer's disease.

Despite the lack of success in direct efforts to isolate putative MS and ALS causative agents, the discovery by Gajdusek, Gibbs, and their co-workers of the transmissible nature of Kuru and of the long latency time between contact with the agent and the development of the disease has spurred efforts in this area. The mechanisms by which a virus might attack an organism, either a human being or an experimental animal, and cause a disorder which persists, while exhibiting no significant symptomatology at the time of infection, but be reactivated or released from latency many years after the initial insult, is clearly important. Therefore, the mechanisms by which these viruses can persist are being actively investigated by grantees from NINCDS.

An obscure disease of sheep called "scrapie" has been an important area of research. Transmission studies and neuropathological examination of brain tissue suggest that scrapie is a prototype for the spongiform encephalopathies of man, i.e., Kuru and Creutzfeldt-Jakob disease. Prior to the transmission of the Kuru and C.J. disease to chimpanzees by intracerebral inoculation of infected brain both of these diseases were classified as "degenerative abiotrophies" of the nervous system.

To date, the chemical nature of the scrapie agent remains obscure. The unusual physio-chemical properties of the scrapie agent and its slow replication in the absence of any detection by host defense mechanism suggest that scrapie is a novel infectious entity. Unlike other viruses, the scrapie agent cannot be visualized by electron microscopy and its presence does not provide a detectable immunological response.

This research program is directed in part toward understanding the "slow" nature of the scrapie agent. Because the present assay for scrapie requires determination of an endpoint by titration in mice over nine months, they are attempting to purify the scrapie agent and use this preparation to explore chemical and immunological assay systems. The purification and subsequent elucidation of the chemical structure of the scrapie agent promises to bring new concepts and techniques to several areas of molecular biology and medicine.

The results of experiments conducted by an investigator at the University of Wisconsin support the nucleic acid nature of the scrapie pathogen. Furthermore, the buoyant density suggests that the scrapie-specific DNA is bound to another macro-molecule, perhaps a protein. No one has yet been successful in adapting this neuropathic agent to a cell culture system. Cell line SHB retains a constant level of infectivity if cell replication is arrested, whereas, cells allowed to continue dividing, gradually lose infectivity. However, there is no indication, at least through 35 days, that the scrapie agent is actually replicating in these arrested cells. The SHB cells and others called HN-JCI cells were pretreated with nerve growth factor (NGF) before exposure to scrapie. NGF appeared to have no effect on the ability of the SHB cells to support scrapie replication, but the HN-JCI cells treated with NGF contained 100 times less infectivity when bioassayed 14 days postinfection than did untreated cells. This result may have been due to the observed toxic effect of NGF on these cells.

They also reported a retinopathy in scrapie-infected hamsters, which may be directly induced by the agent rather than the result of retrograde degeneration from central neural damage. The higher titer of infectivity in the optic nerve at each interval tested suggests that the retina is infected via nerve fibers from the brain (centrifugally.) This possible migration of infectivity in nerve fibers is also a reasonable explanation for the previous findings of infectivity in corneal epithelium in TME-infected hamsters.

They have also adapted C.J. disease to the guinea pig but are proceeding cautiously with the characterization of the agent(s) because of the risk of human infection. The results on subcellular fractionation of C.J. disease in guinea pig brain show a very similar distribution to that seen in scrapie-infected hamster brain, although the titers are much lower.

The above experiments indicate that scrapie-like agents can be reisolated rather easily after passage in subhuman primates. This contrasts sharply with human C.J. tissue which is not readily pathogenic for laboratory rodents. These results do not support speculation that C.J. disease is caused by humans becoming infected with sheep scrapie.

An investigator at the University of Minnesota is studying herpes simplex virus infections of the nervous system and has largely defined the progression of the infection as it moves from a peripheral site of infection through the periphal nerves via axoplasmic flow, to the sensory ganglia, into the spinal cord and finally to the brain. This progression can be altered at the sensory ganglia where the virus can establish a latent infection in the neurons. Further, due to the greater control which can be exercised in a tissue culture environment, they plan to develop an organ culture model of rat skin and dorsal root ganglia. Initial efforts were devoted to characterizing the ultrastructural and electrophysiological aspects of this model. Next, these same parameters will be examined after MacIntyre virus infection of the cultures. Finally, they will determine the effects of various components of the rat's immune system (antiviral antibody, complement, interferon, rat "T" and "B" lymphocytes, and macrophages) on the pathogenesis of the virus.

Studies of temperature sensitive (ts) 472 chandipura virus (CV) infection of mice has revealed that this mutant produces striking primary demyelination when inoculated into 3 to 4 week old Swiss mice.

An investigator at Northwestern University is working on a system that may be an important model for certain human diseases, such as ALS or MS. Inoculation of 3 to 4 week old Balb/c mice with temperature sensitive (*ts*) G41 vesicular stomatitis (VSV) produced a subacute neurological disease characterized by weakness and hind limb paralysis in 90% of the mice. These clinical findings lasted from 8 to 28 days postinfection. Only 10% - 15% of the mice died as a result of infection, and almost all clinically affected mice recovered from their illness They were able to show that viru recovered from these infected mice was *ts* and by co-cultivation isolatable for up to 3 to 4 weeks in brain and spinal cord tissues. These studies lend strong support to the hypothesis that *ts* mutants of VSV possess not only the capacity to attentuate *in vitro* infection but also to produce subacute to chronic central nervous system (CNS) disease. The implications for human diseases are obvious and important.

The overall objectives of an investigator at the University of Southern California, are to study the effects of viral infection on spinal cord-muscle tissues *in vitro* from a developmental, functional and metabolic points of view. Factors which might influence the susceptibility and outcome of viral infection in spinal cord-muscle cultures are studied. Recent work supported by this grant has been centered on improving culture methods for motor neurons and defining the neuronal infection by avian encephalomyelitis virus (AEV).

Thymidine kinase (TK) Herpes Simplex virus (HSV) studies by an investigator at Milton S. Hershey Medical Center is aimed at the demonstration of the importance of HSV TK expression in the establishment of ganglionic infection. Viral TK function was not important for ocular infection (a site of dividing and potentially dividing cells) whereas for infection of nondividing neurons TK functions was important. These results demonstrate the role of a viral function in infection and are of great significance in considering the pathogenesis of HSV infections.

The ultracentrifugal inoculation (UCIN) procedure is a valuable means of of enhancing HSV infectivity, apparently by concentration of virus onto monolayer cells. The trigeminal ganglion negative studies support the contention that the latent HSV infections are non-productive. Details of the UCIN procedure have been explored and it appears to be a procedure which may be of great value for the isolation of low levels of infectious virus in experimental and possibly clinical situations.

Very little is known about the interaction of papovaviruses with human hosts, although these agents are ubiquitous in human populations, have a definite role in a lethal central nervous system infection, progressive multifocal leukoencephalopathy (PML), and have a possible role in human neoplasia. In particular, little information has existed as to the natural route of transmission of papoviruses, the character of the initial infection which these agents produce, and the ability of these agents to produce persistent infection. Because papovaviruses have strict species-specificity, it has not been possible to answer these questions using human papoviruses in laboratory animals.

The studies undertaken by an investigator at the University of Virginia disclosed gained information hopefully applicable to human disease by evaluating the biologic behavior of a parallel papovavirus, K virus, in its natural host, the mouse. Experiments to date, designed to minimize erroneous data caused by contamination with other mouse viruses, have delineated the natural route of inoculation and distribution of infection for a member of the papovavirus group. During the last year they have documented that this papovavirus regularly involves the central nervous system of its natural host during acute infection and is capable of persisting in brain and other organs for protracted periods of time despite the development of high titers of specific antibody. In addition, studies have shown that immunosuppression results in reactivation of infection and in involvement of brain. These findings raise questions as to whether similar involvement of brain may occur during other papovavirus infections of animals and man and whether similar central nervous system involvement may occur in immunosuppressed human patients and find rare clinical expression as PML.

At Cornell University, explanations are being sought for the ability of canine distemper virus (CDV) to cause persistent brain infection and demyelination in dogs. These studies are undertaken with a view to study an animal model of subacute sclerosing panencephalitis and possibly other demyelinating diseases such as multiple sclerosis. Three strains of CDV that differ in their capacity to induce subacute encephalitis in specific-pathogen-free (SPF) beagles were singled out for this study. The careful analysis of a disease process may reveal means of its prevention or treatment. Explanations are sought in these studies for the ability of CDV to cause persistent infection and demyelinaton in dogs. By comparing experimental allergic encephalomyelitis (EAE) with CDV induced demyelination in dogs they emphasized the importance of persistent virus in early demyelination which could be followed by autoallergic reactions later. Early subclinical demyelination in multiple sclerosis has not been studied, and a similar process might be involved in that disease.

Once the importance of persistent virus in the intiation of demyelination has been established, the next question to ask would be: what causes the virus to persist? By studying interferon levels in serum of dogs after infection with different CDV strains, they were able to differentiate between infection with attentuated (no interferon) versus virulent CDV (injected with interferon). In contrast, interferon was present in CSF of dogs with persistent brain infection for extended time periods. It is not yet known whether this phenomenon represents a cause or a result of persistent infection; however, it might serve as a marker for persistent CDV brain infection.

Lymphocyte mediated immune responses require further analysis before their importance in viral persistence can be evaluated. They appear to correspond with humoral antibody responses and may not be a significant marker. The study of antigenic differences in CDV strains and the immune response to them in relation to persistent infections has only begun. Progress has been made in production and partial purification of dog interferon. When more purified interferon becomes available new in vivo and in vitro studies will be initiated on its significance in induction of persistent infections.

Canine Distemper Virus is also being studied by an investigator at Ohio State University. The overall objective of this project is to utilize the CDV as a model to study the pathogenesis of virus-induced demyelinating encephalitis as it may apply to subacute sclerosing panencephalitis (SSPE) and multiple sclerosis (MS) in man. The study is directed toward elucidation of persistent neurological infection by CDV in gnotobiotic dogs utilizing morphological, virological, immunological and biochemical approaches.

These studies are designed to increase our understanding of the mechanisms of demyelination induced by R252-CDV. Of particular importance is the 21-day pathogenesis study. Results indicate that, for the first time, it is possible to reliably induce persistent infection and accompanying demyelination with an incidence approaching 100%. This break-through will permit careful sequential analysis of developmental aspects of this lesion and associated immunological and virological correlates of it. The combined viral and immunological studies are valuable adjuncts to the in vivo studies in that they will permit further dissection of factors responsible for persistent CNS infection.

The studies of visna virus being carried on at Johns Hopkins show quite clearly that visna is incorporated into the genome of the host cell and that somehow the expression of this virus is blocked. Visna is capable of rather rapid change or mutation within the host, and at different stages of development within the host animal, the virus produces different kinds of protein.

Visna is a naturally occurring chronic neurological disease of sheep caused by a persistent infection with a retrovirus. It is the prototype of slow infectious with predominantly inflammatory pathology similar to that caused by conventional agents. An experimental model has been established in Icelandic sheep by an investigator at the University of Pennsylvania, who is conducting an ongoing study of the pathogenesis of this classical slow infection. These studies have established that the infection is widespread but very few cells are infected, only minimal levels of free infectious virus are released, and infection is often limited to latently infected cells. Antibody is raised only slowly, appearing in serum at 13 months as measured by complement fixation (CF) and neutralizing antibody (N) tests. Brain lesions evolve quite rapidly in the first month after infection, but then become stabilized with very irregular exacerbations and highly variable incubation periods. The lesions can be prevented by immunosuppression and are probably mediated by a cellular response to virus-specified antigens. There are a number of antigenic variants of the virus distinguishable in the N test. Serolological studies suggest that, following infection with a single serotype, other variants may appear at irregular intervals.

Sheep infected with visna virus, despite the fact that they have an appropriate acute cell mediated immune response, develop a relapsing and remitting progressive disease and die. The investigators hypothesize that this progression of neurological disease in the face of attempts by the host to defend itself may represent the cumulative effect of clinically apparent attacks induced by intermittent release of antigenically altered virus. Thus, the phenomena of lysogeny (incorporation of the viral genome into the host genome) and antigenic drift, may combine to provide a unique mechanism which explains the acute episodes of remitting and relapsing disease. This kind of mechanism has been proposed for multiple sclerosis, subacute panencephalitis, and certain forms of senile dementia.

An investigator at the University of California, San Francisco, is studying the synthesis of visna virus nucleic acids. This work is directed toward elucidation of the molecular basis for the persistence of the virus, and the slow evolution of disease. The current hypothesis is that persistence and the cours of the disease may be explained by restriction in virus gene expression *in vivo*; therefore the experimental efforts are focused on the analysis of virus gene expression in infected tissues. This analysis of necessity requires methodology which will quantitate synthesis of virus DNA and RNA in cells in tissues. For this reason considerable effort has been devoted to *in situ* hybridization, and they can now assess viral RNA synthesis at single copy levels in cells. Studies in progress are aimed at increasing the sensitivity of the assay for DNA to comparable levels, and to developing an assay for viral proteins that is both quantitative and more sensitive than immunofluorescence. With these methods they can determine on what level virus gene regulation is affected *in vivo*. In particular they think that these experiments will demonstrate that virus production is regulated under both restricted and permissive conditions of replication by gene dosage effects.

In a series of pioneering experiments by the Hopkins group it was first shown that adult mice immunosuppressed with cyclophosphamide not only were prevented from developing fatal CNS disease after infection with LCM virus but they also became asymptomatic virus-carriers just like mice infected at birth. Moreover, all of these carrier mice, about a week after receiving lymphocytes obtained from spleens of syngeneic virus-immune mice, developed fatal CNS disease that was clinically and histologically indistinguishable from the classical LCM produced in immunocompetent adult mice. Third, the production of LCM by the transferred spleen cells failed to occur if they were depleted of their T lymphocyte component. These results provided the first clear-cut evidence for the participation of virus-specific T lymphocytes in producing CNS immunopathology and they set the stage for further experiments addressing the conceptually important question of whether a sub-population of T lymphocytes is induced during viral infections that has the specialized function of singling out infected host cells as specific targets for destruction.

The continuing primary goal of a research project at Johns Hopkins University is to identify and study virusspecific cellular immune responses which influence the establishment, course and outcome of viral inflections having the potential to cause neurologic disease. Initial studies that began about 10 years ago, have demonstrated that a variety of animal hosts, including mice, rats and monkeys, develop severe and often fatal paralytic disease if infected at a time when their immune system was rendered temporarily dysfunctional by treatment with the immunosuppressive drug, cyclophosphamide. In contrast, similarly infected animals that were not immunosuppressed usually recovered, often without exhibiting clinical CNS disease. A microscopic comparison of CNS tissues taken at various stages of infection, from groups of normal and immunosuppressed animals yielded two striking observations. First, the extent of neuronal destruction caused by replicating virus was far greater in immunospressed animals and, second, in these same animals, the influx of inflammatory cells that normally accompanies tissue destruction by virus was markedly reduced or absent. Comparative measurements of infectious virus in CNS and other tissues revealed levels in immunosuppressed animals, that were 1000 or more times greater than the levels present in animals with an intact system. These findings, coupled with the fact that in immunosuppressed animals an antibody response specific for the infecting virus was either undetectable or delayed, comprised some of the first experimental evidence to support the already existing notion that the outcome of viral infections was decided in a "race" between the virus and the host's immune defenses. In other words, if in the course of its replication, a virus destroyed too many host cells before being checked and eliminated by the developing immune response, death was the inevitable result, whereas infections involving relatively few cells before immune elimination occurs could go undetectable clinically yet confer longlasting specific immunity to re-infection. Another important point that emerged from these early studies was that immunosuppression could abrogate the innate resistance to certain neurotropic viruses that for many years had been correlated with variables such as host maturity or species, a particular route of infection or a small infecting dose.

The demonstration that immunosuppression with cyclophosphamide could cause normally selflimiting CNS infections to become progressive and lethal provided the means for assessing more definitively the relative contribution of the humoral and cellular components of the immune response to recovery from viral infections. By using inbred strains of genetically identical mice as experimental hosts it is now possible to determine whether the potentiating effects of immunosuppression can be reversed by the adoptive transfer of virus-neutralizing antibody or lymphocytes from syngeneic virus-immune donors. When this was done using immunosuppressed mice infected by a peripheral route with West Nile virus, a member of a large family of viruses that causes encephalitis in man, antibody alone was capable of preventing mortality even when administered after the infection had extended to the CNS. Immune donor lymphocytes were equally effective but only when transferred before virus invaded the brain. Thus, in this animal model of human disease, the humoral component of the anti-viral immune response appears more important in recovery than does the cellular component.

One model of viral-induced CNS disease that has intrigued and fascinated both virologists and immunologists is the acute fatal infection of adult mice produced by lymphocytic choriomeningitis (LCM) virus - so named because of the striking mononuclear cell inflammatory response which develops rapidly and almost exclusively in the leptomeninges and choroid plexus of the brains of infected animals. This histologic picture, together with violent convulsions, may be seen for several days prior to death but only when mice are inoculated with certain strains of LCM virus by an intracerebral route. If given by a peripheral or extranueral route, the virus usually fails to reach the brain, and causes an inapparent infection that immunizes the mice against a subsequent intracerebral virus challenge.

As shown some years ago, LCM virus by itself is not cytopathic when it replicates in mouse cells cultured in vitro and, in nature, the agent is indigenous to certain colonies of wild mice which harbor it for life, vertically transmitting it to successive generations in the absence of disease. Man is occasionally an accidental host after contact with infectious urine or feces of such mice. From the results of earlier studies it was suspected that the immune response to LCM played a decisive role in producing CNS disease since, in the laboratory, fatal LCM occurred regularly only when virus was given to adult mice whose immune system was intact but not when given to immunologically immature neonatal mice. The latter, like their free-living counterparts, became persistent virus carriers for life.

Idiopathic polyneuritis or polyradiculoneuritis, otherwise known as Guillain-Barre syndrome, Landry's ascending paralysis, or Landry Guillain-Barre-Strohl syndrome is, since the advent of vaccination against polyomyelitis, the most common cause of acute severe generalized paralytic disease in man. Although a relatively common condition affecting the population at a reported annual prevalence of 1-1.6 cases per 100,000 population, it has recently come to public attention in the United States as a presumed complication of vaccination against "swine flu".

The overall objective of the research constructed at Sidney Farber Cancer Institute is to examine the relationships between determinants of the major histocompatability complex of man (HLA), swine flu immunization dependent immunological phenomena, and the presence or absence of the Guillain-Barre syndrome. Advantage is taken of the background of this laboratory in the immunogenetic analysis of experimental auto-immune neurological disease, the study of thymus derived cell function and precise indepth studies of HLA.

Bacterial meningitis remains a very significant problem in the antibiotic era. This disease has increased in this community during the past several years and in particular, a striking increase in infection due to Hemophilus influenzae, type b has been observed. Recently, an increased incidence of meningitis due to Group B beta hemolytic streptococci in children over 1 month of age but less than 6 months of age has been observed. It has been documented that there are selected clinical and laboratory findings that one can detect at the moment of admission that permit prediction of the likelihood that any given patient may experience sequelae of meningitis.

The studies at Johns Hopkins University have expanded previous observations on the pathogenesis of H. influenzae b meningitis in the infant rat model. Since prevention of H. influenzae type b invasive disease is the ideal way to protect children against the serious morbidity and mortality resulting from meningitis, the use of the infant rat provides an approach to exploring the induction of protective immunity on an experimental basis. Although caution must be exercised in extrapolation of data from animals to man, a valid experimental model can provide information that cannot be readily obtained by other approaches.

The studies at Baylor College of Medicine document in a prospective fashion for the first time that prior treatment with antibiotics should not preclude making a specific etiologic diagnosis of meningitis provided a complete evaluation of cerebrospinal fluid is performed and this is coupled with concurrent analysis of blood, CSF and urine utilizing countercurrent immunoelectrophoresis.

A high frequency of inappropriate secretion of antidiuretic hormones during uncomplicated bacterial meningitis has been documented. In particular, specific measurements of antidiuretic hormone concentration in serum and CSF in children with bacterial meningitis have been made for the first time. This data, coupled with finding that hyponatremia correlates significantly with various sequelae of meningitis should lead to more intensive and aggressive ancillary measures designed to limit excessive fluid administration. It is hoped that the future studies may reveal ways in which ADH secretion can be altered therapeutically.

In conclusion, these studies have demonstrated that appropriate early and vigorous treatment of the patient with bacterial meningitis can limit both neurologic and psychometric sequelae of the disease. The studies also have demonstrated the requirement for very careful control of fluid balance as an important adjunct to the therapy of patients with bacterial meningitis. They have demonstrated the utility of countercurrent immunoelectrophoresis as a routine procedure for establishing the rapid etiologic diagnosis of this disease. They also have demonstrated dramatic deficits in host response in children less than 17 months of age referable to both humoral antibody and polymorphonuclear leukocyte function.

MUSCULAR AND NEUROMUSCULAR DISORDERS

The muscular and neuromuscular disorders sub-program supports research in Muscular Dystrophy (MD), Myasthenia Gravis (MG), and Peripheral Neuropathies. Some research relevant to Amytrophic Lateral Sclerosis (ALS) is also included. As of July 2, 1980, 146 grants were active. Three research program projects are included: one devoted primarily to basic research in neuromuscular disorders, a Muscular Dytrophy center and the third specializing in peripheral neuropathies. The program project devoted to neuropathies is due for competing renewal in FY 1982. Total FY 1980 cost for these activities is $11,730,340. Eighty-seven applications were received and 68 were approved. Twenty-six new and 14 competing renewals were funded with a total cost expenditure of $1,486,301 for new and $1,433,301 for competing renewal grants.

Muscular and neuromuscular dysfunction is directly responsible for disability in patients suffering from a wide variety of diseases of the central and peripheral nervous system. Research on the pathophysiology and treatment of these disorders constitutes a major portion of this program's extramural research support portfolio. There has been remarkable progress in the identification of various pathologies resulting in myasthenia gravis and in the management of this disease(s). Most of the regular research grant support is for basic studies of the neuromuscular system. There is currently a wave of interest in synaptology and properties of normal and diseased membranes. Another focus of interest is muscle physiology and motor control. Much of this work utilizes a classical electrophysiological approach to the study of both individual units and aggregated systems of motor units. The latter adds to the knowledge of how muscles work in concert. Two other foci of research activity are pathophysiology and protein metabolism of muscle tissue.

Synapses are excellent structures for investigating the biology of cell secretion, which operates in them by exocytosis, as it does in glandular elements. Using electromicroscopic techniques one investigator has photographed neuromuscular junctions that have been frozen rapidly at different intervals, before, during and after single nerve impulses. He has successfully imaged neurotransmitter secretion and uptake across a synapse.

An investigator at Colorado University is studying and comparing the ultrastructural consequences of axotomy in the ciliary ganglion of the chick, the electrophysiological properties of pituitary cells, and the 'noise' spectrum produced by neurotransmitters at inhibitory synapses in the brain of the Lamprey.

There is research dealing with the relation between end-plate potential (e.p.p.) and the underlying conductance change produced by the neurotransmitter acetylcholine (ACh) in the post-junctional membrane. The relation between voltage and conductance can be expected to be non-linear but there has been some question as to the extent of the now-linearity. A number of theoretical considerations have been published but no careful experimental measurements have been made. In mammalian (mouse) muscle the results were as expected for a restricted area of synaptic contact on a semi-infinite cable. Frog muscle, on the other hand, showed less non-linearity than expected for such a model, behaving instead like a spherical cell with a synaptic input. The deviation from theory in frog muscle appears to be related to the fact that the end-plates, instead of being restricted to a point contact, extend along the muscle for distances of half a space contant or more.

These studies are aimed at obtaining a better understanding of two aspects of intercellular communication. First, they hope to obtain more information about how neurotransmitters and peptide hormones are released from cells. Secondly, the studies of post-junctional conductance and synaptic noise should provide us with information about how transmitter substances interact with post-junctional receptors on their target cells.

Investigators at Northwestern University are working on elucidating the mechanism whereby various drugs and chemicals interact with the end-plate receptor/channel. In recent studies, they have found that certain guanidine derivatives such as methylquanidine and amylguanidine block the endplate in a manner dependent upon the current. Since a variety of guanidine and other ammonium derivatives are available, and since the potency spectrum for endplate seems to be related to molecular size and specific groups, further exploration of the mechanism of endplate block of these compounds is expected to provide a clearer picture of the end-plate receptor channel with respect to the pore dimension, gating mechanism, ionic selectivity, and kinetic behavior. In order to accomplish the goal, a variety of advanced electrophysiological techniques are employed including voltage clamp, noise analysis and single channel recording. This study may provide the basis on which the actions of a variety of pharmacological and therapeutic drugs on synapses in the central nervous system and ganglia can be interpreted. It is also expected that the results will provide useful guides for elaboration of therapeutic agents acting on the nervous system.

Other studies have shown that apparent synaptic potentials seen in axons behave in manner consistent with a model of "backward" coupling across synapses. One study deals with "seizure" activity of cells in the spinal cord, which is accompanied by prolonged depolarization of the reticulospinal axons. Another focuses on characteristics of presumed chemical inhibitory and excitatory synaptic potentials. Both the prolonged depolarization and the synaptic potentials have characteristics usually attributed to chemical transmission. Because responses are dependent on membrane potential, it has been assumed that they involve a chemically mediated conductance change. Analysis of these data suggest that both the prolonged depolarization and apparent excitatory synaptic potential amplitude varying with membrane potential, can be explained quantitatively by the intrinsic properties of the axons. The paradox of apparent chemical synaptic potentials without the morphological presence of adequate numbers of appropriate synaptic connections may thus have been resolved.

A series of studies of cortical motor potentials in man and monkey is almost completed. In the macaque a self-paced hand closure is associated with a slow potential in the motor hand area and in area 6 adjacent to the midline. The potential in the motor hand area preceeds the onset of movement and has the earliest latency of any of the potentials recorded from these areas. In man, the areas mentioned above also show a slow potential, but in addition, the slow potential is recorded in an area of cortex anterior to area 6. Studies on motor potential in humans have been carried out in epilepsy patients undergoing surgery for intractable seizures. One interesting observation was a lack of electrical excitability of motor cortex for producing movement in children between ages 1 1/2 to 4 years. This has been ascribed to immaturity of the cortex. There may be disparity in ontogenic development between sensory-evoked responses and cortically-induced movement.

Other studies are adding information about the way motoneuron pools are organized and controlled. It is supposed that the organization is changed in neurological disease or trauma; however, current knowledge of the normal organization is not yet sufficient to allow these changes to be used diagnostically. Studies of normal motor pool organization will allow a better understanding of how motor units and muscles with very different mechanical properties are integrated into smooth movements. It was shown that recruitement order is not as stable in response to mixed inputs as it is to the homonymous spindle input generally studied. This could explain reversals in recruitment order previously reported. Studies of rank order of the entire pool, however, confirm a general pattern of recruitment order according to motoneuron size. The one clear reversal of this pattern appears to be a presynaptic effect and not a result of direct facilitation by large motoneurons.

Studies have shown that human muscles may be controlled in a different way. Force in biceps is graded by recruitment of units throughout the force range while rate coding is less precisely controlled. Irregular discharge patterns of motor units would strongly affect force output of this muscle at high force levels, since rate coding is apparently the sole mechanism of force modulation.

An investigator at the University of Minnesota is studying the fine structure of muscle spindles. Capillaries within muscle spindles have certain morphologic and probably functional characteristics that are similar to capillaries within peripheral nerve and are therefore an extension of the blood-nerve barrier. The spindle is a convenient, visible, easily isolated structure containing only two or three capillaries. Because of their accessibility, intrafusal capillaries could provide a model system in which to test certain features of the blood-nervous system barrier, recognizing, of course, that there are certain regional pecularities.

The work is also significant in that it expands our knowledge of the normal morphology and physiology of spindles. This allows for a more sophisticated comparison of spindles from humans and hamsters with diabetic neuropathy, humans and mice with hypertrophic polyneuropathy and humans and mice with anterior horn cell disease, that are under study in this laboratory.

Regeneration of muscle spindles in grafted muscle and freeze fracture preparatious of primary sensory endings are also being studied. Unlike the events occurring at the motor terminals that are rapidly becoming more understandable, the processes at sensory terminals are almost unknown. The most popular thoughts are that distortion of the membrane components open the gates, change electrocyte flow across the membrane, and give rise to the receptor potential. This process is not believed to involve a chemical transmitter.

Another research project utilizes experimental computer simulation and analysis to study the coordination of muscles during propulsion by animals and human subjects in the execution of a jump. Jumping was chosen because of its suitability for analysis by a combination of experimental measurements and optimal control techniques and because it is a good starting point for a more in depth study of neural and muscular control of movement. The quantitative methods developed will be useful later in the analysis of human gait. Long term goals are to use these quantitative techniques to develop rehabilitation systems for the physically handicapped and quantitative tests for the evaluation of physical dexterity in patients, and to assess the efficacy of drugs and other therapeutic programs.

An investigator at Washington University is studying how muscle contraction in normal and diseased muscle is controlled at the cellular and molecular level. This includes an understanding of the relationship between membrane depolarization and calcium release; how Ca^{++}, pH, (MgATP), ionic strength and other intracellular variables affect contractile protein interaction; how mechanical variables such as sarcomere length affect contractile properties and excitation-contraction coupling, and how paralysis is produced in an animal model of hypokalemic periodic paralysis.

Measurement of the relationship between isometric force and sarcomere length in cardiac muscles is important in helping us understand factors which limit force production at short muscle lengths. This decrease in force with decrease in length is the cellular basis of Starling's law in the heart, which is important in the intrinsic regulation of the heart. Experiments on the effects of length changes during contraction on calcium transport are important in terms of helping elucidate the mechanism of "deactivation" in muscle, so vital for many muscles, particularly cardiac muscle, which shortens during ejection of blood. In addition, these measurements shed light on the mechanism by which calcium activiation leads to force production in these muscles. It is possible to infer calcium bound to filaments from these studies and draw conclusions about activiation.

Experiments on muscles from potassium-depleted rats provide information which will be directly applicable to patients with hypokalemic periodic paralysis, as this appears to be an excellent animal model of this disease. There are many questions yet to be answered before full understanding of this and related diseases involving changes in serum potassium is achieved. These studies help elucidate the effects of hormones, like insulin, on membrane conductances and their role in determining inexcitability and paralysis in muscles from these potassium-deficient rats and in patients with hypokalemic periodic paralysis.

The use of behavioral technologies in the management of patients with neuromuscular and convulsive disorders is expanding rapidly. The Neurological Disorders Program in cooperation with the Johns Hopkins School of Medicine and the John F. Kennedy Institute for the Handicapped sponsored a conference in 1980 to develop a state-of-the-art report on the use of behavioral therapies for the alleviation and control of these and related disorders. The report will be distributed widely to researchers and practitioners.

MUSCULAR DYSTROPHY

As of July 2, 1980, 19 grants were active in the Muscular Dystrophy (MD) sub-program, including one research program project. The total FY 80 cost expenditure in support of these activities is $1,601,754. Eighteen applications were received and 14 were approved. Of these, 6 were new and were funded for $326,036.

Muscular dystrophy refers to a group of chronic, progressive, genetically determined diseases that are characterized by weakness and wasting of the voluntary muscles. The rate of progression is markedly variable from type to type.

A high percentage of patients come from families with a history of muscular dystrophy. The hereditary defect may be transmitted by either parent. In Duchenne muscular dystrophy (DMD), the most common type of dystrophy, the disease is inherited as a recessive trait, and transmitted by clinically unaffected females almost exclusively to their male progeny.

Symptoms in children include frequent falling, difficulty ascending stairs, waddling gait, great difficulty in rising from a lying or sitting to a standing position, apparent increase in the size of the affected muscles, particulary in the calf, and contractures of the affected muscles. While the contractures may cause suffering, pain is not a feature of the disease itself. The diagnosis is usually made between ages 3 and 6 and the patient often stops walking by age 12. Not a few patients also have cardiac problems and are slow mentally. Most of these patients expire before adulthood, often of intercurrent infections.

In adults the muscles affected earliest may be those of the shoulder and/or hip girdles, upper arms, thighs, and back, and in certain forms of the disease, those of the face.

It is estimated that some 200,000 men, women, and children in the United States are suffering from muscular dystrophy. Nearly two-thirds of the known victoms are children between the ages of 3 and 13.

There is no effective treatment for muscular dystrophy itself. To date, none of the wide variety of diets and drugs administered to patients has shown a significant or lasting effect on the course of the disease. Physical therapy has limited value in delaying contractures but does not otherwise affect the course of the dystrophic process. Antibiotics may prolong the lives of children who would otherwise succumb to respiratory infections.

A number of etiologies have been suggested. The neurogenic and vascular theories have not been well-supported. A possible explanation for DMD, as for other genetic disorders, is a widespread independent expression of a metabolic defect in many tissues, with muscle being the principal target. It is reasonable, as in other recessively inherited genetic disorders, that DMD is due to mutation in a single enzyme or a small number of enzymes with similar amino acid sequences near the active sites in the enzymes. The descriptions in recent years of structural or biochemical defects in cell membranes of erythrocytes, platelets, and muscle suggest that the enzymatic defect is expressed subcellularly by a change in cell membranes.

This membrane hypothesis has received particular support in the case of the myotonic disorders. There is evidence of biochemical abnormalities in the muscle sarcolemma and RBC membrane in patients with myotonic dystrophy, and there are convincing data that the myotonic phenomenon itself is due to a conductance abnormality in the surface membrane.

A number of investigations have focused upon the properties of the cell membrane in Duchenne dystrophy, especially on adenyl cyclase, an enzyme which is localized in the plasmalemma and which reflects changes in plasmalemmal biochemistry. Alterations in cells other than skeletal muscle have been identified. It remains to be determined whether the enzyme, the receptor, or the membrane environment is the site of abnormality.

A diffuse decrease of internal membrane particles has been demonstrated in Duchenne dystrophy using freeze-fracture techniques. Expression of this defect in cultured muscle cells would be of considerable interest because it would indicate a genetically determined abnormality inherent in the muscle cell, possibly in the plasma membrane. Erythrocyte membrane properties of DMD patients are also being studied by biophysical methods.

Abnormal leakage and enzyme release has been detected using muscle from DMD in tissue culture. Since muscle cells in tissue culture resemble normal fetal muscle in many respects, increased enzyme leakage in Duchenne may be present at an early stage of differentation. In addition, scientists are extending analyses of steady-state tension responses and incorporating tests for fast and slow twitch fibers into studies of human muscle diseases.

Investigators have measured maximum force (Po), sensitivity to substrate, and Ca^{++} sensitivity, in over 200 single human skinned fibers. Po was significantly less than normal in the majority of fibers. The data on Po provide the first direct evidence that muscle weakness involves a defect in contractile protein function before significant loss of muscle mass has occurred. It is postulated that low tension in single skinned fibers prepared from Duchenne muscle are linked to structural disorders in myofilaments. More specific tests of this hypothesis are planned.

Hereditary muscle disease, closely resembling human muscular dystrophy, has appeared in a number of animal species, notably mice and chickens. Both of these species are under intensive investigation, allowing scientists to perform controlled experiments which are impossible to carry out in human beings. A great deal of valuable information has been derived from these animal models.

The differentiation of skeletal muscle involves cell recognition and fusion. This observation, and consideration of the hypothetical existence of a membrane defect in muscular dystrophy, has led workers to examine the topography, composition, and metabolic turnover of plasma membrane proteins in differentiating cultures of normal and geneticlly dystrophic embyronic chick breast muscle. No topographical differences have been found between normal and dystrophic fibroblasts, myoblasts, or myotubes.

A group of investigators is attempting to characterize the cellular and humoral immunodeficiencies in the Storrs strain of muscular dystrophic chickens, and to establish the relationship of the immunodeficiencies to the pathogenesis of the muscular dystrophy phenotype. PAGE (poylacryalamide gel electrophoeresis) and IEF (isoelectric focusing) analyses of the soluble fraction from the pectoralis major and the posterior latissimus dorsi muscles of dystrophic chickens reveal quantitative protein and isozyme differences when compared to normal age and sex matched controls. These procedures hold promise as one element of a pathological index established on the basis of several different parameters. The finding of two major genetic disorders, muscular dystrophy and immunodeficiencies, in the Storrs strain of muscular dystrophic chickens may be important. On the basis of immunogenetic analyses of the two disorders, the investigator has demonstrated that the two traits are genetically separable, and postulates that the time of onset and degree of severity of the muscular dystrophy phenotype is altered in the absence of the cellular immunodeficiency. This points up the importance of genetic studies in interpreting data on common membrane defects such as those seen in human myotonia and Duchenne muscular dystrophy. These studies suggest an important role for the immune response in myopathies. If the immunodeficiency could be corrected or alleviated it might have a beneficial effect on the muscular dystrophy phenotype.

MYASTHENIA GRAVIS

As of July 2, 1980, 14 grants were active in the Myasthenia Gravis (MG) sub-program. The total costs expenditure in support of these activities is $1,415,110. Fourteen applications were received and 10 were approved. Of these, 2 new and 3 competing renewals were funded, costing $143,923 and $518,349, respectively.

MG is a chronic neuromuscular disease characterized by rapid fatigue and weakness of voluntary muscles due to defective transmission of the nerve to muscle impulse. The disease tends to accur at an earlier age in females and later in males. In recent years marked advances in the management of patients with this disease have been achieved due to increased understanding of the disorder. Not too many years ago, MG patients died within the first few years of their illness. Today, under proper supervision, many can live virtually normal lives.

Therapies such as anti-acetylcholinesterase (ACH) drugs, long-term, high-single-dose, alternate-day prednisone, and thymectomy in selected cases may make MG the most successfully managed neuromuscular disorder.

The technique of plasmapheresis is being used to remove antibody from the blood of some MG patients. A bypass is introduced into the patient's blood system so that blood can flow through a continuous centrifuge. This separates the cellular components of the blood from the soluble fraction, the plasma. The cells are then allowed to re-enter the circulation with fresh plasma or plasma substitute. The technique allows the replacement of the entire plasma of the patient without disturbing the important cellular components of the blood. Unfortunately, the antibody slowly returns. Plasmapheresis is used to treat only selected, severely afflicted patients, who do not respond adequetely to other therapeutic modalities.

The neuromuscular junction was first identified as the general site of the disorder of MG on the basis of the beneficial effects of anti-acetylcholinesterase medication. This was confirmed later by the physiological finding of a decrease in the amplitude of miniature endplate potentials (mepp's) and the morphological observation of simplified postsynaptic folds of human myasthenic neuromuscular junctions. However, it was not until 1973 that the precise defect was identified as a decrease of available acetylcholinesterase receptors (AChRs) at the neuromuscular junction, by means of an ^{125}I-αBungarotoxin binding method. Further, it was shown that reduction of available AChRs can account for all the pathophysiological features of MG, as demonstrated by a model of experimental blockade of AChRs with cobra toxin. However, it remains to be demonstrated that the deficit of AChRs at the neuromuscular junction of a given patient correlates directly with the severity of clinical weakness.

An autoimmune abnormality was suggested by numerous indirect observations, including the association of MG with other autoimmune diseases, abnormalities of the thymus gland, and the reduction of serum complement levels. An animal model of experimental allergic myasthenia gravis (EAMG) produced by immunization with purified AChR provided further support for the concept of an autoimmune disorder directed against AChR.

The finding of antibodies against AChR in the serum of up to 80% of patients with MG and the demonstration that passive transfer of these antibodies could reproduce the basic features of MG in recipient mice strongly suggested an important role for humoral antibodies in the disorder. The active immunoglobulin fraction has been shown to be IgG in the mouse passive transfer model, and IgG has been demonstrated at neuromuscular junctions of myasthenic patients by electron microscopy.

Considerable progress has been made in elucidating the mechanisms by which IgG from myasthenic patients reduces AChRs. Using a mammalian tissue culture system it was found that IgG from myasthenic patients accelerates the degradation rate of AChR up to three times of normal. In addition, it produces blockade of active sites of AChRs. However, it does not affect synthesis of/or incorporation of AChRs into the muscle membrane. The ability of IgG from myasthenic patients to induce accelerated degradation occurs not only in tissue culture, but also at intact neuromuscular junctions in vivo. It appears to depend on the divalence of the IgG molecule which cross-links AChRs. The cross-linked AChRs are preferentially selected by the muscle cells to undergo rapid degradation.

Complement appears to enhance the effects of myasthenic IgG, as demonstrated in the mouse passive transfer system. Further, complement has been demonstrated morphologically at neuromuscular junctions of myasthenic patients, and it has been suggested that complement, possibly in conjunction with macrophages, may damage AChRs and the postsynaptic membrame.

Although anti-AChR antibodies clearly play a key role in the pathogenesis of MG, the relationship between the antibody titer and the patient's clinical status is not straightforward. One possible explanation for these discrepancies may be that differences in the functional ability of the anti-AChR antibodies to induce accelerated degradation, to block receptors and to induce complement-mediated damage may determine the severity of the AChR deficit in individual myasthenic patients.

The role of lymphocytes in the pathogenesis of MG is not yet clear. Several studies have demonstrated that activation, measured by blast transformation, occurs when lymphocytes from myasthenic patients are incubated in vitro with AChR-rich material derived from electric eels or rays. This indicates that lymphocytes from myasthenic patients have been sensitized to AChR. Clearly, lymphocytes from MG patients have been shown to be involved in the production of anti-AChR antibody. However, it is not yet known whether some abnormality of immune regulation contributes to the autoimmune response in MG. In any case, the lymphocytes sensitized to AChR represent a key element in the autoimmune response, that may be vulnerable to specific immunotherapeutic attack.

Another unsettled problem concerns the origin of the autoimmune response in MG. Much circumstantial evidence implicates the thymus. The thymus undergoes hyperplasia or neoplasia in about 75% of MG patients. Thymectomy results in clinical improvement in many patients. The thymus gland contains both immunocompetent cells and muscle-like "myoid" cells which have been shown to bear AChR. The juxtaposition of these cell types suggests that a change in either the myoid cells or the intrathymic lymphocytes could serve to break tolerance and initiate an autoimmune response. However, neither the factors that trigger the autoimmune response nor those that serve to maintain it are yet understood.

Investigators at Johns Hopkins University are studying various aspects of the pathogenesis, physiology, immunology, and treatment of the disorder. They were the first to demonstrate the decrease of AChRs at neuromuscular junctions of myasthenic patients, and also showed that the experimental pharmacologically-induced reduction of AChRs could account for all of the patho-physiological features of MG. They had also demonstrated the pathogenicity of circulating MG immunoglobulins using the mouse passive transfer model, and that its effect was enhanced by complement. They showed that immunoglobulins cause accelerated degradation of AChRs in tissue culture, affecting only the set of AChRs with bound immunoglobulin, and that cross-linking of AChRs by divalent antibodies was necessary for this effect. Furthermore, synthesis of AChRs in muscle culture is not affected by treatment of the cultures with myasthenic IgG, and revealed that accelerated degradation of AChRs occurs at the *intact* neuromuscular junction both *in vivo* and in organ culture. In addition to degradation of AChRs, myasthenic immunoglobulin produced blockade of AChR sites in cultured muscle.

In studying the origin of the disorder in MG, these investigators demonstrated that skeletal muscle cells can be cultured from thymus glands of myasthenic patients and rats, and that these cells bear AChRs. This would support the suggestion that the autoimmune response in MG may originate within the thymus itself. However, they could not reproduce the previously-reported model of MG based on immunization with thymic extract. They have studied the time course of the celluular response in experimental autoimmune MG, showing that the lymphocytes respond to the foreign (Torpedo) AChR used for original immunization earlier than they respond to self (rat) AChR.

Some investigations of the pathogenesis of myasthenia gravis (MG) have been directed toward relating *the mechanisms* of action of humoral anitbodies to the clinical severity of MG in individual patients. Since the number of ACh receptors is decreased in MG skeletal muscle motor endplates, two mechanisms that may be important in producing this effect are: 1) decreased synthesis of ACh receptors, and 2) accelerated degradation of ACh receptors. Accelerated degradation of ACh receptors in myotube cultures has been previously demonstrated. Investigators have demonstrated that MG serum or immunoglobulins decrease incorporation of new ACh receptors into the membranes of fetal muscle in tissue culture.

The objective of the work at the Salk Institute is to elucidate at the molecular level the mechanisms by which nerve, muscles, and glia cells in the nervous system interact with one another. These investigators have developed a tissue culture system utilizing cloned cell lines isolated from the nervous system. They have demonstrated that chemical synapses form between cloned cell lines of nerve and muscle *in vitro*. They are also concerned with elucidation of the defect in an experimentally-induced, myasthenia gravis-like disease. These studies have lead to the discovery that the aceylcholine receptor is degraded at an accelerated rate in the presence of antibody against the acetylcholine receptor. They have also shown that high densities of aceylcholine receptor (i.e. "patches" of AChR) are disaggregated by low calcium concentrations, blockers of energy metabolism and agonists of the receptor. They suggest that high densities of receptor are held together by an active process requiring energy.

Additional research addresses the relevance of humoral antibodies and their role in determining the clinical state of individual MG patients. Several studies were carried out during the past year. Findings include: 1) Anti-ACh antibody titers do not correlate with clinical severity of disease in the populations of MG patients and do not necessarily correlate with changes in clinical myasthenia in individual MG patients. 2) Presumably identical anti-ACh receptor antibodies can have markedly different clinical effects in different individuals. 3) The degree of acceleration of ACh receptor degradation produced by MG immunoglobulins correlates only with the titer of anti-ACh receptor antibodies and not with the clinical state of MG patients. Future work will be directed toward investigation of decreased incorporation of new ACh receptors and the role of "host" factors in determining the severity of clinical myasthenia in MG patients.

Another approach to MG involves studying the effect of the myasthenic process on the endplate and the muscle type. Current data confirm earlier observations that the myasthenic process leads to a deficit of cholinergic transmission. There is also support for the concept that the myasthenic process leads to a change of endplate properties.

Understanding the structure and function of the actylcholine receptor (AChR) is important because the AChR is an achetype for studying neurotransmitter and drug receptors in the peripheral and central nervous system. In particular, an understanding of the structural basis of AChR function may provide a molecular explanation for neuromuscular transmission, may help to provide a more rational basis for drug therapy and may help explain developmental processes in synapse formation before innervation and after denervation. Immunochemical studies of AChR structure and function can also help bridge the gap between the many systems used to study various aspects of AChR structure.

Study of experimental allergic myasthenia gravis (EAMG) has proven its importance by providing a model for illuminating the once inscrutable pathological mechanisms of MG. It continues to be valuable as a model for study of pathological mechanisms and for studying therapy. In addition EAMG is valuable as a tool for producing anti-AChR antibodies and studying their effect in vivo on AChR function and metabolism. Understanding the pathological mechanisms in MG and EAMG is important not only as an end in inself, but also because EAMG is the prototype for other autoimmune anti-receptor diseases such as diabetes.

It is not known why myasthenic patients produce globulins that bind to a variety of cellular and subcellular components. It has been suggested that there may be an immunodeficiency disorder that predisposes to bacterial and viral infection. A genetic predisposition is suggested by the familial incidence of myasthenia gravis of 3%, compared to an incidence in the general population of 0.01%, and increased prevalence of HL-A8 histocompatibility antigen in myasthenic patients, although the concurrence is far from uniform.

The most recent studies, and especially the animal model of experimental immune myasthenia gravis, make it likely that antibodies to acetylcholine receptor are responsible for the neuromuscular block of myasthenia gravis. This hypothesis has not yet been proven, but when it is, the criteria for an anuto-immune disease will be fulfilled. The more difficult question of why these antibodies are released remains to be answered.

Drug induced myasthenia gravis has been observed in patients treated chronically with d-Penicillamine for rheumatoid arthritis or Wilson's Disease, and less frequently in patients treated with procainamide for cardiac arrhythmias. These and other drug induced myasthenic "syndromes" are under active study in a number of centers. Clarification of the mechanism of action of d-Penicillamine and other drugs may provide valuable information concerning the pathogenesis of myasthenia gravis and other autoimmune diseases.

At present, most patients with MG can be treated successfully by various combination of: a) anticholinesterase drugs; b) immunosuppressive therapy; c) thymectomy; and d) antibody depletion. Although effective in most cases, these methods rarely cure, and often have significant side-effects. Since some patients with refractory myasthenia gravis may respond poorly to any or all of these measures, new therapeutic modalities are also needed. Ideally, therapy should be directed at the specific autoimmune abnormality in the myasthenic patient. Studies of the effect of other alterations in the immune mechanism on experimental and human myasthenia gravis are in progress which may prove to be relevant to other autoimmune diseases as well. In view of the promise of greater understanding of the various immunological abnormalities which may explain the variations in the clinical MG, more specific and effective immunotherapeutic strategies will be developed.

There are approximately three-and-one-half-million diabetics in the United States. About 10% of these have symptoms of painful burning, numbness, weakness, or paralysis of the extremeties, or even more serious neurological problems. The causes of these symptoms are not known and treatment is directed toward good control of the diabetes. The Neurological Disorders Program (NDP) encourages research in this area. Only a limited number of regular research grants focus on these problems.

As of July 2, 1980 10 grants (including one research program project)were active in the peripheral neuropathies sub-program. The total costs expenditure in support of these activities is $1,116,766. A total of 5 applications were received and 4 were approved. Of these, 3 new grants were funded at a total cost of $174,448.

The NDP supports a specialized research center at the Mayo Clinic and Foundation in Rochester, Minnesota which coordinates multidisciplinary research on human and experimental neuropathies. Investigators are focusing on new approaches and techniques that combine morphologic, electrophysiologic, immunologic, biochemical and physical research techniques. A system has been developed to quantitate the sensory modalities in man. There are a number of morphometric studies of human and animal biopsy and autopsy tissues. Electrophysiological studies of nerve function utilize the traditional clinical methods as well as newer techniques such as in vitro single nerve fiber investigation. There are studies of axonal flow and endoneural pressure. Immunologic methods are being used to assign cellular responsibility for segmental demyelination and to assess the roles of viruses in inflammatory neuropathy. Studies of lipid composition of nerve and the effect of modification of membrane lipids are underway by lipid chemists. The largest single responsibility of the center is for studies of diabetic neuropathies; however, other neuropathies to be explored include a number of genetically determined diseases in man and animals, human and experimental heavy metal intoxication, and inflammatory nerve disease. One ongoing program studies whether there is an accumulation of alcohol sugars in damaged fibers in diabetes. Another seeks to establish if there is a decrease in myoinositol in peripheral neurons. Diabetics are often not "tightly controlled" in regard to blood sugar levels in order to avoid hypoglycemia and there is concern that the increased blood sugar levels may interfere with neuronal metabolism.

The principal objective of the study at Ohio State University is to define the role of axoplasmic transport in the pathogenesis of diabetic neuropathy. The velocities in the "BB" Wistar rat are determined and thus far they have been able to correlate changes in anterograde flow rates with degrees of hyperglycemia. Morphologic studies continue as well. Further analysis of the tibial nerve and nerves of the intrinsic foot muscles may prove helpful in reaching a definitive conclusion about the nature of the structural changes.

Previous investigations at the New Jersey Medical School have demonstrated that peripheral sensory nerve terminals are more sensitive to damage by certain neurotoxic agents than their motor counterparts. Consequently, neurological dysfunction in these toxic peripheral neuropathies results, in part, from inadequate and/or incorrect proprioceptive information from sensory terminals (i.e. primary afferent terminals). This could compound the neurological manifestations by impairing the integrative capactiy of spinal segmental reflexes and relay synapses providing proprioceptive information to higher centers.

Morphological studies of toxic acrylamide neuropathy have revealed a defect in the primary afferent terminals rather than in the spinal motoneurons per se. Taken in concert, these findings demonstrate the predominance of sensory nerve impairment in the early stages of this toxic peripheral neuropathy.

Moreover selective inhibition by acrylamide of an enzyme neron specific enolase (NSE) provides a rational approach to the study of biochemical mechanisms of acrylamide neuropathy. The finding that NSE is inhibited in vivo suggests that it may play a role in the etiology of the neuropathy.

The overall objective of the research in Mississippi is to determine the genetic linkage relationships of a spinocerebellar ataxia gene inherited in an autosomal dominant pattern in a large kindred in which preliminary data indicates close linkage to the human lymphocyte antigens (HLA) histocompatibility complex. In addition to HLA, glyosalase I, pepsinogen-5, blood group P, and phosphoglucomutase-3, all possibly within measurable linkage distance on human chromosome 6, are studied. Valuable information may be obtained both for mapping chromosome 6 in man and for establishing linkage relationships of a disorder roughly equivalent in social impact to Huntington's Chorea and ALS. Thus more precise genetic counseling might be available.

An investigator is studying Friederich's ataxia and lipoamide dehydrogenase. Friedreich's ataxia is inherited in a recessive pattern. Carriers cannot be identified nor can the disease be predicted. Abnormalities of the enzyme lipoamide dehydrogenase (LAD) have been found in tissue homogenates of some patients. The LAD is probably present as a component of multi-enzyme complexes, especially the pyruvate and ketoglutarate dehydrogenase complexes. They are exploring the possible pathogenetic relations between abnormal LAD and the ataxia and hope to develop tests for diagnosis, carrier detection, prediction of disease, and ultimately approaches to therapy. Positive results may encourage future studies of therapy with ketogenic diets. Other proteins in the multienzyme dehydrogenase complexes may be defective, also. The finding of a single major isoelectric band of platelet LAD will encourage further studies of the platelet enzyme. If the new method produces a similar result in other tissues, the procedure should expedite additional studies of the basic biochemistry of mammalian LAD.

With respect to the Guillain-Barre Syndrome, researchers report several findings that have important implications for future investigations. It was found that the rat is a far more suitable animal in which to study experimental allergic neuritis (EAN), a model for Guillain-Barre Syndrome, than are rabbits, guinea pigs or monkeys. Furthermore, the P_2 protein of peripheral nerve myelin is the neuritogenic antigen when present as a lipid-protein complex. It is hoped that the study of EAN will eventually provide the insight needed to elucidate the induction and possible suppression of the Guillian-Barre Syndrome in humans.

NEUROENDOCRINE AND NEUROPEPTIDE MECHANISMS

The late Geoffrey Harris demonstrated that the anterior pituitary gland was under the control of the hypothalamus and this fact, more than any other, opened the field of neuroendocrinology. In retrospect, it is odd that another large set of facts showing the importance of the endocrine system for the brain were so neglected. That patients with thyroid dysfunction thought slowly was well known, and that psychoses could occur with excessive or deficient thyroid function ("myxedema madness") or in the course of Cushing's disease (excessive adrenal cortical function) was well known. That early castrates showed no sexual interest was an obvious fact. The introduction of adrenocorticotropic hormone and adrenal steroids into clinical medicine in the early 1950's was followed by multiple descriptions of psychotic disorders in some of the treated patients. Despite all these facts, there was at the time remarkably little interest in the mechanisms in the nervous system which underlay these remarkable alterations in behavior.

Hypothalmic Peptides: The regulation of anterior pituitary hormone secretion is dependent on the release of hypothalamic substances into the capillaries of the median eminence. Three such peptides, thyrotropin-releasing hormone (TRH), luteinizing hormone-releasing hormone (LHRH), and somatostatin have been isolated and their structure has been worked out. TRH stimulates thyrotropin and prolactin secretion, LHRH releases luteinizing hormone and follicle-stimulating hormone, and somatostatin inhibits growth hormone and thyrotropin release. Evidence also exists for corticotropin-releasing factor, GH-releasing factor and another prolactin-releasing factor separate from TRH, but their structures are at present unknown. Pituitary prolactin secretion is predominantly inhibited by the hypothalamus under physiological conditions and there is growing evidence that dopamine acts as the principal prolactin-inhibiting factor.

Evidence indicates that the actions of the identified hypothalamic hormones are not restricted to regulation of anterior pituitary hormone secretion. Thus, the three peptides mentioned above have been found in many brain regions. These substances modify neuronal activity when applied to individual neurons in several brain regions. These facts lead to the suggestion that these peptides may act as synaptic transmitters or neuromodulators. More recently it has been discovered that many of the anterior pituitary hormones are also manufactured in the brain.

The question of the functions of brain peptides has been further clarified by the demonstration that several other peptides, isolated from hypothalamic or other brain regions (substance P, neurotensin, the opioid peptides, bombesin, angiotensin, and gastrin, for example) also have neuroendocrine effects. Each is known to be located in the "endocrine" part of the hypothalamus, the median eminence. Thus the administration of substance P and neurotensin to rats has been shown to result in release of both growth hormone and prolactin. In addition, intraventricular administration of the peptides with opium-like actions, beta-endorphin and enkephalin, results in growth hormone and prolactin secretion. Few of these effects seem to be due to direct pituitary actions since the peptides are largely ineffective in stimulating hormone release from the anterior pituitary in the test tube. This has led to the suggestion that these peptides act in the brain to regulate neuroendocrine responses.

Effects of Neurotransmitters on Pituitary Hormone Secretion: The secretion of the hypothalamic peptides is thought to be modified or regulated by the actions of brain neurotransmitters. This evidence is derived largely from *in vivo* studies of the effects of systemic or intraventricular administration of drugs that affect synthesis, reuptake or degradation of neurotransmitters. In particular, the monoamines (dopamine, norepinephrine, epinephrine, serotonin, and histamine) have been shown to influence anterior pituitary secretion by effects mediated at hypothalamic or other CNS sites. Acetylcholine and gamma-aminobutyric acid also influence hypothalamic regulation of pituitary secretion.

Future Outlook: During the past few years, at least 12 separate peptide substances have been structurally identified and shown to be present in significant quantities in the brain. Almost without exception, the highest concentration of these substances is in the hypothalamus, with particularly high concentrations in the neurovascular zone of the median eminence. Several of these peptides have clear functions in relation to anterior pituitary control; others, although shown to influence hormone secretion, may function primarily in other regions of the brain related to sensory conduction, pain mechanisms, and behavioral responses. Receptors for many of these substances are now being searched for in the brain tissue and pathways linking peptidergic systems are currently under investigation using neuroanatomical tracing techniques and immunocytochemistry. Important advances in this area will require detailed analysis of: 1) The neuroanatomy of peptidergic pathways, 2) the neurophysiological effects of peptides and a definition of their sites of action, 3) neuropharmacological studies to identify receptor sites on neural tissue and to identify agonists and antagonists that might have therapeutic implications, 4) analysis of the hormonal and cerebral spinal fluid distribution and effects of peptides, and 5) analysis of the behavioral effects induced by these substances.

To role of peptides in neurobiologic function has received increasing attention in recent years. It appears that most peptides are distributed widely throughout the brain and act by attachment to peptide receptors to initiate neurobiological events; these effects result in neurophysiological, biochemical, and behavioral manifestations. A particularly exciting area of development is the association between peptides and pharmacological effects. Although naturally occuring peptides have a short duration of action and cross the blood-brain barrier in small quantities, structural modifications, particularly with the addition of D-isomers into the peptide chain, can result in marked prolongation of effect and in successful transport across the blood-brain barrier. Therapeutic potential of these agents is only presently being tested. A recent report suggests that vasopressin administered intranasally can significantly affect memory function in normal adults and have reparative effects in patients with dementia. This kind of work is of critical importance to establish therapeutic potentials for these agents. Indeed for reasons which are not obvious nearly all the hypothalamic peptides tested affect memory functions.

Discovery of the structure and functions of the hypothalamic peptides has already resulted in a number of significant demonstrations of pathophysiology and it is unquestioned that numerous others will follow. The use of hypothalamic hormones for stimulation of anterior pituitary function has led to the unequivocal demonstration that certain forms of panhypopituitarism are due to congenital or developmental deficiency or failure of function of hypothalamic peptidergic systems. Thus, many cases of idiopathic or familial hypopituitarism can now be assumed to be due to failure of biosynthesis or release of the appropriate hypothalamic hormone. Some of these disorders, such as Kallman's syndrome, are associated with other disorders of neurologic function, in particular olfactory deficiency. Congenital anomalies of midline cerebral structures also result in hypothalamic failure due to congenital absence of hypophysiotropic hormones. These conditions are rare and the importance of the discovery of hypothalamic hormones is that their treatment is now potentially possible with centrally active peptides.

The demonstration that dopamine deficiency is important in the pathogenesis of Parkinson's disease and the analysis of other monoamine neurotransmitters in patients with Huntington's diseases, Gilles de la Tourette's syndrome, various choreas and torsion dystonias, and the Lesch-Nyhan syndrome have sparked interest in the role of small molecular weight substances in the pathogenesis of such diseases. A recent report indicated that the angiotensin-converting enzyme is abnormal in Huntington's disease, implicating a potential abnormality of peptide biosynthesis in this disease. These observations, taken together with the rapidly expanding information on peptides, make it important to further analyze peptide mechanisms in neurological disease. Use of immunocytochemical techniques, which are applicable to postmortem tissue, analysis of peptide levels in brain taken from patients with neurological disease, and further studies of receptors in such patients bear promise of resulting in significant clinical advancement.

Neurological Disorders of Aging

The program currently supporting research in the neurobiology of aging is composed of five sections. These are: Parkinson's Disease, Huntington's disease, Alzheimer's disease, other disorders of aging and General Studies.

Parkinson's disease resulting from the death of dopamine containing neurons in the substania nigra is primarily being studied from a biochemical point of view (25 grants, $2,982,500). A broadbased approach ranging from the genetic and biochemical to the psychological and sociological is being pursued in the Huntington's disease program (18 grants, $2,382,000). Research in the Alzheimer's disease area offers much fertile ground for biomedical exploration. The present program contains research of a multidisciplinary nature (12 grants, $900,000). The program in General Studies includes work on the structural and functional alterations of the aging nervous system, (17 grants, $1,993,500).

The total program contains 72 active research grants totalling $8,258,000. During fiscal year 1980 the program received 98 applications for research support, of which 25 were paid for $2,784,000. This included the successful initiation of two "Huntington's Research Centers Without Walls" for $1,100,000.

Parkinson's Disease and Parkinsonism

Parkinson's disease, the most common form of Parkinsonism, is an illness almost unique to those over the age of 50. About one-half million people in the United States are affected by Parkinson's disease, or about 1% of the population over age 50. Prevalence and incidence rates remain the same in all races and throughout the world where good epidemiological studies have been conducted. Men and women are equally affected.

Evidence to date indicates that Parkinson's disease is not hereditary nor is it the product of an environmental toxin or pollutant. A large study of monozygotic twins, one of each set with Parkinson's disease, was conducted by investigators at Mt. Sinai Hospital in New York. The study demonstrated that in no instance were both twins of a set affected. There is also no evidence that offspring of Parkinson's disease patients have a greater risk of developing the illness than anyone else. Since husbands and wives share similar environments, it is not likely that a dietary or environmental pollutant is the origin.

Whatever does cause Parkinson's disease remains a mystery. Dopamine containing neurons in the substantia nigra die, causing a depletion of this important neurotransmitter. Gradually, clinical signs of tremor, rigidity, and bradykinesia begin to appear, becoming more severe as time passes. Many patients suffer gradually diminished intellectual faculties. The symptoms of Parkinsonism can result from neuroleptic administration, as a postencephalitic sequelae, from arteriosclerosis and from a variety of diseases and intoxications.

The majority of grants on Parkinson's disease focus on the biochemistry of the illness and the ways in which neurotransmitter systems transmit messages in the brain areas most affected. It is not surprising that the biochemistry of this disorder should preoccupy scientific attention; after all, discoveries about the deficiencies of dopamine in Parkinson's disease patients led to breakthroughs in our understanding of neurochemistry and pharmacology in brain disorders in general.

Clinical Studies and Clinical Centers

Now that the initial excitement of discovering that decreased dopamine stores lead to the symptomatology known as Parkinsonism has subsided, it has become increasingly apparent that administration of L-dopa to increase endogenous dopamine stores is not sufficient to treat the disease completely. Unpleasant side effects and an erratic effectiveness of the treatment, known as the "on-off" phenomenon have pushed scientists to develop new treatments. Many of these compounds act in concert with L-dopa to increase its potency.

Investigators at New York University have had a long-standing and productive research program dedicated to discovering new treatments for Parkinsonism. They have had some success using dopamine agonists such as bromocriptine and lergotrile. Both drugs were effective in relieving tremor in Parkinsonian patients and also in VMT-lesioned monkeys, but lergotrile was shown to have significant hepatotoxic effects. Several ergoline derivitives were evaluated for their dopamine agonist activity in animals, but only two drugs, pergolide and lisuride, were shown to be potent DA agonists and long acting agents in the experimental animal models. Preliminary clinical studies with pergolide appear to be positive. This project will explore many aspects of DA receptor function, particularly identifying DA receptor sub-types, and exploring the specificity of action of DA agonists at different DA receptors. The relationship of this neurotransmitter and its receptors to the pathogenesis and therapy of Parkinson's disease will be pursued. The nigral graft model and the possible role of epinephrine systems in DA-mediated behaviors will also be explored.

Studies are now under way at the Columbia Presbyterian Hospital to test a new therapy for Parkinsonism. Working on a theory that the adverse side effects of L-dopa treatment, including the debilitating "on-off" phenomena, stems from the conversion of dopamine to o-methyldopamines, the investgators propose to use U-0521 or other catechol-o-methyl transferase inhibitors to use as an adjunct treatment in Parkinsonism. The medication should hopefully prolong the sequestration of levodopa in erythrocytes and thereby enhance the efficacy of L-dopa therapy in Parkinsonism. The investigators will further explore the role of the red blood cell as a possible vehicle of L-dopa transfer and as an agent for taking up L-dopa, activities which may account for some of the variability in blood levels of the drugs. Experimentation with COMT inhibitors will be done in rats and in Parkinson's disease patients.

In order to improve the therapeutic efficacy of existing treatments for Parkinson's disease, investigators at the Illinois Institute of Technology are experimenting with the use of metal chelates bound to L-dopa as an aid to transporting the amino acid across the blood-brain barrier. At the University of Rochester, other scientists are exploring the effects of chronic levodopa, phenobarbital, and diphenylhydantoin administration on the gastrointestinal tract, since these drugs are absorbed in larger part by the gastric mucosa prior to reaching their effective sites in the brain. The structural and functional studies being carried out may give insight into the toxic side effects of these drugs and possible adverse effects of taking them in combination.

At the University of Colorado a "Center for the Study of Basal Ganglia Disorders and Neurotransmitter Function" has had a long and productive history. Neuropharmacological, neurochemical, electrophysiological and immunocytochemic techniques are used to explore normal and abnormal functioning of the basal ganglia. The major thrust of the program is a multidisciplinary study of neurotransmitters and neuromodulators in the CNS with major emphasis on the basal ganglia and the nigrostriatal dopamine pathway. Four research areas examine the neurochemical and electrophysiological changes in basal ganglion function brought about by acute and chronic nerve stimulation and agonist or antagonist drug administration. Special attention is given to the roles of presynaptic and postsynaptic receptors. The effects of chronic drug administration and, as a related theme, neuronal plasticity are the focus of a number of research projects. Studies include aspects of neuronal growth, differentiation and regeneration, and the influences of calcium dependent regulator proteins, glycoprotiens and growth factors on these processes. Neurotransmitter biosynthetic enzymes are viewed as indices of neuronal growth and development.

Clinical studies in this program attack the problem of tardive dyskinesia, a troublesome iatrogenic disorder which is a pernicious consequence of prolonged neuroleptic use. Evoked and spontaneous EEG responses will be correlated with urinary biogenic amine metabolites. Clonidine and propranolol, which do not give rise to TD, will be tested as possible therapeutic agents for schizophrenic patients with tardive dyskinesia. Since patients show a variable vulnerability to develop TD, and there is at present no way to differentiate those that are at higher risk than others, investigators will attempt an intermittent L-dopa challenge in neuroleptically treated patients to see if it is prognostic of impending tardive dyskinesia.

Mt. Sinai School of Medicine is the home of a clinical "Center for Research on Parkinson's Disease and Allied Disorders". A multidisciplinary program of clinical and basic research focuses on clinical trials with therapeutic agents, measurement of body fluids, detailed observations of the natural history of the disease and the biosynthesis of possible new treatments. A tissue bank stores autopsy brain tissue which is analyzed with a variety of histochemical and neurophysiological techniques. The role of viruses as possible etiological agents is being pursued. Basic biochemical studies focus on amino acid metabolism in the basal ganglia and on synaptology, among other areas.

Cornell University is in the process of terminating a large program project grant with many pharmacological studies aimed at developing new and improved treatments for Parkinsonism and epilepsy. The effect of chronic choline administration were studied in eight patients with Parkinsonism under a double blind protocol. Results suggest a central cholinergic pathway may not play a major role in the induction of L-dopa-induced dyskinesia and in the dementia associated with Parkinsonism. In fact, chronic choline administration can raise central cholinergic activity, thus exacerbating Parkinsonian symptoms. Raising cholinergic stores was moderately therapeutic for two patients with neuroleptic induced dyskinesia, but one remained unchanged. Seventeen Parkinsonian patients, some treated and others not, were tested for manganese levels which were found to be normal. Manganese tissue levels were measured in 52 treated epileptics and 30 controls. Blood and hair manganese was significantly lower in treated epileptics than in controls. A relationship seems to exist between high seizure frequency and low manganese levels. Manganese, which serves as a membrane stabilizer, may contribute to the biochemical precipitants of seizure activity. Future studies suggest that seizure activities may markedly alter the tissue distribution of injected manganese in favor of certain tissues and to the detriment of others, including the brain. Other aspects of this program project focus on the testing of new compunds which could be dopamine agonists and have potential therapeutic value.

Biochemistry and Pharmacology

Given the drive for increased pharmacological tools to treat movement disorders such as Parkinsonism, Huntington's disease, Tourette's Syndrome, dyskinesia and others, the discovery of the clinical efficacy of apomorphine has aroused considerable interest. An investigator at the University of Texas is continuing a program of basic research on the metabolism of apomorphine (APO) and N-n-propylnorapomorphine (NPA). The two drugs have shown definite promise as clinically useful anti-Parkinsonian agents. The investigators will continue their work developing analytical methods for studying these drugs and their analogs and in metabolites in biological material, and will pursue ways to overcome the deleterious side effects of the drugs, particularly azotemia. Studies will be carried out in the rabbit which seems to be a satisfactory animal model.

Our understanding has jumped rapidly from the initial description of neurotransmitters to the discovery of multiple receptors for these transmitters. Investigators at the University of Colorado are exploring the densities and properties of receptors for dopamine, norepinephrine, and acetycholine in the caudate nucleus. They are looking for the possiblity of multiple sub-types of receptors for each of these transmitters and will therefore attempt to localize these receptors to their specific cell populations.

At Yeshiva University in New York, investigators in a Center research program are also studying the role of biogenic amines in neurological disorders. Clinical and basic research studies at the Center are aimed at further elucidating the dopamine (DA) neuronal receptor system. These investigators have pharmacological evidence of three types of dopamine adenylate cyclase receptors in the striatum, anterior limbic cortex, and frontal cortex. Ligand binding studies are being carried out within parts of the extrapyramidal system to determine the properties of dopamine adenylate cyclase receptors including supersensitivity and subsensitivity. Explorations will be made of the behavioral effects in rats with denervation supersensitivity after nigrostriatal lesioning. As part of a project to study the dopamine system as a whole and its interactions with other neuronal systems, the effects on the DA neuronal system of peptide transmitters and GABA will be examined. The investigators are using a variety of sophisticated techniques including 2-Deoxyglucose autoradiography and histofluoresence to learn more about the sites of action of DA agonists and the anatomy and processes of DA cells. Clinical studies have included patients with other diseases which affect aminergic activity, such as Tourette's syndrome, tardive dyskinesia, action myoclonus, and others.

While some investigators are invloved with understanding and improving upon current therapeutic regimens for Parkinson's disease, other scientists are looking more broadly and basically at the neurochemical, histological, and anatomical systems of the brain which are most affected in Parkinson's disease and related basal ganglia disorders. At the University of California at San Diego, a research program is mounted to analyze the organization of monoamine neuron systems in the mamalian brain and their response to injury. The maturation of the catecholamine neuron system and its plasticity in response to drug induced and mechanical damage during development and in maturity is being examined.

Neurotransmitter function in the globus pallidus of monkeys is the target of investigation for scientists at the University of Texas. The effects of acetylcholine (weak to moderate excitant), dopamine (weak excitant), serotonin and substance P (little or no effect), gamma-aminobutryic acid (strong inhibitor), taurine, glycine, and beta-alanine (inhibitors) on the responsiveness of neurons in the globus pallidus are being measured to determine normative functioning in an area of the brain damaged by a number of extrapyramidal disorders.

At the University of Southern California, Los Angeles, an investigator proposes to examine neurochemical relationships involving the nucleus accumbens, looking at this structure during spontaneous locomotor activity and under drug stimulation. A great variety of drugs will be used to characterize the role of the nucleus accumbens. Scientist at Baylor College will also be studying the effects of drugs on the nucleus accumbens of squirrel monkeys during motor activity.

Scientists at the VA Lakeside Hospital have made an animal model of Parkinson's disease by lesioning the nigrostriatal pathway in cats and are studying neurotransmitter balance in the caudate nucleus of the lesioned animal. Their theory is that Parkinson's disease results from an imbalance among the cholinergic, dopaminergic, gabanergic, and serotoninergic systems enervating this area.

The substantia nigra is the object of study for another investigator at the University of California in Los Angeles. This investigator has made real progress in determining the cytoarchitecture, projection patterns, and functional significance of acetylcholinesterase (AChE) containing neurons in the subtantia nigra. Evidence has been presented that AChE is contained within the dopamine neurons in the pars compacta of the substantia nigra, possibly to inactivate acetylcholine released from cholinergic afferents to the nigra. The investigator seeks to discover if some cells contain both AChE and dopamine and if these cells differ morphologically from those that carry AChE but not DA. Understanding cholinergic-monoaminergic interactions in the nigra may improve our comprehension of the role of the substantia nigra in Parkinson's and Huntington's disease.

Neurophysiology and Neuroanatomy

Chemical lesioning gives much information about the "wiring diagram" of the basal ganglia, but electrophysiological and anatomical techniques are equally valuable. Scientists at the University of Washington are examining the neurons of the entopeduncular nucleus (ENT) and describing afferents to and afferents from this area, as well as the synaptic actions of ENT cells of several brainstem sites which may link the ENT to the globus pallidus. The investigators seek to clarify what drives the high tonic firing rate characteristic of palladal and nigral basal ganglia output neurons in awake animals.

At the University of Arkansas, investigators are also using neuorphysiological and anatomical techniques to analyze the organization and function of the motor systems in the cat. The aim of this research is to determine the intrinsic synaptic organization of the neurological substrates involved in preparation for movement. In previous years the investigator has established that the "motor" cortex in the cat sends a some what topographical projection into the caudate nucleus. Current research is focused on the relationship of the basal ganglia, including substantia nigra and motor cortex to the mesencephalic locomotor region.

An investigator at The Johns Hopkins University is utilizing electrophysiological and anatomical methodology to explore the motor functions of the basal ganglia. In normal and lesioned monkeys, scientists seek to further clarify the normal functions of the basal ganglia in the regulation of movement and posture and to unravel the pathophysiologic mechanisms underlying movement disorders in man. Trained monkeys are given a visuomotor tracking task while neurons in key brain areas are monitored as the monkeys perform a limb movement. Cells will also be recorded during passive limb manipulations and trained hand and eye movements. The underlying pattern of muscular activity during abnormal movements in primate models is also under investigation. This work comprises some of the best and most exciting single unit analyses of basal ganglia activity in awake monkeys done by an expert in the field.

Huntington's Disease

Huntington's disease, a fatal degenerative hereditary condition, is a disorder of the basal ganglia closely related to Parkinson's disease. While Parkinsonism produces tremor and rigidity, Huntington's disease causes uncontrollable chorea, and gradual loss of the capacity to walk, talk, swallow, and maintain oneself independently. Patients are dysarthric fairly early in the illness, and the majority show some degree of dementia, usually early in the illness becoming quite severe toward the end of the illness. Profound emotional disturbances mimicking schizophrenia and manic depressive disorders may also occur. Huntington's disease is transmitted as an autosomal dominant gene and usually manifests itself between the ages of 35 and 40 years. Children comprise 10% of cases. Treatment is merely palliative and most often entails the administration of dopamine blockers or antagonists. There is no test to determine if a child of a Huntington's disease patient is carrying the lethal gene before symptoms of the illness appear. Patients generally live 10 to 20 years following symptom onset. Biochemically, the disease is characterized by reduced stores of GABA, glutamic acid decarboxylase (GAD), ACh, substance P, angiotensin II converting enzyme and a variety of other neurotransmitters and neuromodulators. There is almost total loss of the small neurons of the caudate nucleus and putamen as well as cortical atrophy, giving rise to a typical picture of enlarged ventricles and sulci on CAT scans.

Genetic Studies

A number of investigators are attempting to identify the abnormal gene that is responsible for the host of physical and mental symptomatology that characterizes Huntington's disease. Based on the genetic prediction that a mutant protein would produce an abnormal charge or weight compared to its homologous gene, and that this difference could be detected through the use of 2-dimensional gel electrophoresis, a scientist at the City of Hope National Medical Center in Durate, California, has been screening over 2,000 gels from the multiple brain areas, fibroblasts, red blood cells, and other non-neural tissues. An abnormal double major spot with two satellite spots was finally located in a perchloric acid extract of the putamen and caudate of an HD patient. A similar mutant protein was found in the brains of some patients with classical schizophrenia but not with other neurological diseases. Controls did not have this protein, nor did all HD patients. The investigator has hypothesized that HD and schizophrenia may be allelic variations of the same gene. Work is now being carried out to isolate and characterize these mutant proteins and test for their presence in a larger sample of patients with different disorders.

Another way to locate the HD gene is to search for a marker in close proximity to it on the chromosome. Investigators at the University of Rochester are looking for possible linkage or allelism of the genes for plasma cholinesterase (E1 and E2) and Huntington's disease. The study stemmed from a report from Britain that there is an increased incidence of the rare E1 gene and C5+ variant of cholinesterase in HD patients. The association may be due to actual linkage or to a modification of the expression of the gene. This research may offer clues as to future research directions, including early diagnosis and treatment.

The fact that Huntington's disease is a genetic disorder can be used to increase the power of scientific investigations. Different genes or alleles of the same gene giving rise to similar phenotypic expression can still produce biochemical differences. Using tissues from a large pedigree of affected individuals mitigates against genetic heterogeneity which can confuse the interpretation of research findings. The validity of any finding purporting to be an expression of the gene product or closely linked to it can be quickly tested by seeing if the finding segregates with the HD gene in a pedigree. Again, a large pedigree is needed. Investigators also have need for different types of research subjects. In a disorder as relatively uncommon as Huntington's disease, and with family members so widely dispersed geographically, a centrally located data bank of pedigrees is an invaluable aid to research. A contract for a Huntington's Disease Roster was given to the University of Indiana to develop such a roster, in response to a recommendation of the Commision for the Control of Huntington's Disease and Its Consequences. The Roster can match together family members with different names and from disperate states, thus creating much larger pedigrees . It can also select specific families needed for particular research projects and serve as an intermediary between the scientist and the subject.

Studies of Non-neural Tissues

For many years, Huntington's disease has been considered strictly a brain disorder. In recent times, however, the question arose as to whether the HD gene might produce modifications of non-neural tissue. Scientists from the University of Kentucky have been in the forefront of demonstrating that the HD gene may well cause a generalized membrane defect. Subjecting erythrocyte ghosts to analysis by electron spin resonance(ESR), scientists have discovered an alteration in the physical state of membrane proteins in HD patients, as compared to normals and other neurologic disease controls. The W/S ratio was altered in HD patients and HD blood cells showed an increased tendency to form stomatocytes. Increased sialic acid was also noted in the HD erythrocyte membranes. A thorough investigation of these findings using ESR, gas-chromotography mass spectrometry, scanning electronmicroscopy and enzymatic analyses is now in progress.

Other indications that HD might involve a generalized membrane defect have come from studies of skin fibroblasts. Investigators at the University of Oklahoma are exploring biochemical alterations in fibroblasts from HD patients. GAD activity and GABA pool size is abnormal in HD fibroblasts. The uptake and kinetics of neurotransmitters in the fibroblast cultures are being compared with neuronal cultures. This technique may provide a "window "on on brain functioning and permit a variety of studies not ethically possible
now.

Another investigator at Duke University is pursuing his preliminary data which indicate alterations in cell attachment and protein glycosylation in HD fibroblasts. In particular, glutamine was found to be toxic to HD fibroblasts leading to changes in morphology and eventual cell death; these effects are partially reversed by glucosamine. On the basis of these and other observed abnormalities, the investigator suggests that HD fibroblasts express a membrane defect due to abnormal glycosylation of proteins and that this impaired glycoprotein synthesis may be correctable by a diffusible factor in serum. His work proposes to characterize these differences further, and to pursue the hypothesis that the enzyme responsible for glucosoamine synthesis, fructose-6-phospate glutamine transaminase, is the defective metaboloic step in producing the disease.

At the University of Washington, in Seattle, other investigators are studying plasma membranes isolated from skin fibroblasts in an attempt to correlate changes of fluidity and structural modifications in the membrane with the age of the donor and with the aging of cells in culture. The actions of flourescent probes in isolated plasma membranes will be compared with an analysis of membrane lipid protein composition in order to derive a model of the fibroblast plasma membrane. This project will hopefully demonstrate if there are changes in membrane fluidity and composition which correlate with cell aging or with the presence of a disorder such as Huntington's disease. Other investigators at the University of Indiana will also be doing mapping experiments to determine the regional distribution of cholinergic, GABAergic and glutamatergic pathways within the striatum. Interrelationships among these neuronal systems in the rat striatum will be examined.

Ever since the revolutionary work of Gajdusek and Gibbs pushed scientists to consider more unconventional etiologies for chronic degenerative neurological disease, the role of virology and immunology in neurologic disease has received increased attention. It is certainly conceivable that a virus could become integrated into the genome to produce the symptoms and Mendelian inheritance pattern of Huntington's disease. A scientist at the University of California is attempting to explore this hypothesis. His current work is aimed at characterizing a cellular immune response in HD patients which was discovered in his laboratory. Using the mixed lymphocytyes inhibition assay (MLF), this scientist discovered that lymphocytes from HD patients appear to be immunologically sensitized to HD brain tissue, but not to brain tissue from normals or other patients. This finding may be due to the leakage of antigens through the blood brain barrier due to brain deterioration or to the presence of a possible specific HD brain antigen.

Animal Models

Animal models have always been important in the understanding of the etiology, pathogenesis, and possible treatment of disease. HD is no exception. Very recently, a new animal model was created by the injection of kainic acid, a powerful glutamate analogue, into the striatum of rats. The kainic acid produces a selective degeneration of striatal intrinsic neurons, and neurochemical and histologic alterations in the nigro-striatal circuit that closely mimic those found in HD. Fibers of passage are less affected by the kainate, and the chemical has no effect if cortical-striatal pathways are severed.

An investigator at The Johns Hopkins University School of Medicine is continuing his work on the elaboration of the lesioning effects of kainic acid. In vitro measurements will be made of the specificity of receptor binding of kainic acid and kainic acid-induced release of labeled neurotransmitters from prelabled slices of hippocampus, striatum, and cerebellum. In vivo studies will focus on the effects of kainic acid injections on local brain energy metabolism. An important element of the in vivo experiments will be efforts to "rescue" vulnerable tissue through pretreatment with a variety of anesthetic and anti-convulsant drugs. This research may some day lead to prophylactic treatments for patients and individuals at risk for Huntington's disease.

The discovery that GABA and its synthetic enzyme GAD were reduced in the brains of HD patients led to a number of different research questions. Scientists at Harvard Medical School are exploring the neuropharmacology of GABA function through the study of specific enzymes importantly involved in GABA metabolism. Investigators have developed highly potent and specific irreversible inactivators of GABA-transaminase (involved in degradation) and GAD (involved in synthesis). Scientists can thus regulate levels of GABA in tissue culture and in vivo. Using mice and chick embryos and tissue cultures, investigators will create models of HD and other disorders involving GABA metabolism, such as epilepsy. These models can be used to test potentially new treatments that would raise GABA levels. In tissue culture, the role of these two enzymes in the formation of GABAergic synapses and neuronal development can be studied in great detail. The investigators also propose to develop a new mapping technique for GABAergic neurons in culture and in vivo using radiolabled decarboxylase inhibitors coupled with autoradiography.

Interdisciplinary Workshops

One of the most crucial needs in Huntington's disease research is to recruit new investigators to the study of this relatively little known disorder, and to generate new research hypotheses. The Hereditary Disease Foundation has had a ten year program of sponsoring interdisciplinary workshops on Huntington's disease to achieve these ends. Participants range from medical students to department chairmen and span a wide variety of scientific expertise in basic and clinical areas. Four workshops a year will now be supported through a grant to the Foundation.

Huntington's Disease Centers

One of the most exciting initiatives in Huntington's disease research during the past year was the award of two grants to establish "Centers Without Walls", as recommended by the Congressionally mandated Commission for the Control of Huntington's Disease and Its Consequences. Each Center supports clincial and basic research aimed at uncovering the etiology and pathogenesis of Huntington's disease and developing new physiological and sociopsychological treatments for the disorder. One Center is located at The Johns Hopkins University and is composed of a number of different departments within the Medical School, such as psychiatry, neurology, genetics, and the School of Public Health. The program consists of nine clincial and basic research projects. Clinical studies range from case-finding and epidemiological studies, and research on genetic counseling, to the exploration of eye movements as clues to early disease process and diagnosis, and the amelioration of swallowing difficulties. Basic science projects include the localization and measurement of neurotransmitters, neuropeptides, and enzymes in the brain, and the detailed elaboration of the structure and function of the basal ganglia, an area of the brain affected by Huntington's disease, Parkinson's disease, Tourette Syndrome and many other movement disorders. Investigators will attempt to locate all patients and families in Maryland and surrounding states. The J. Earle Moore Medical Genetics Clinic at The Johns Hopkins will provide the clinical "hub" of the "Center".

The Harvard "Center" represents a consortium of departments within different institutions, including Massachusetts General Hospital, McLean Hospital, Boston University, Tufts New England Medical School, the Boston Veterans Administration Hospital, and the University of Massachusetts, and will support 10 scientific investigations in participating institutions. Patients and their families will be seen at clinics in the different Centers. A number of the Harvard projects focus on mapping and measuring levels of neuroendocrines and neuropeptides. These investigators will be developing new procedures for analyzing brain tissues which will be of value for looking at all brain disorders. In addition, they will be examining tissues from patients dying of other devastating brain diseases such as schizophrenia, Alzheimer's disease, Parkinson's disease and others. A team of molecular geneticists at Massachusetts General Hospital will be using recombinant DNA techniques to try to determine the exact chromosomal location of the abnormal Huntington's disease gene. These scientists will be mapping the human genome, uncovering "markers" on chromosomes which will greatly advance the localization of other genetic diseases.

Alzheimer's Disease and Other Dementias of Aging

There was a time when the frailities and foibles of age were thought to be the almost inevitable price for long life. With the impressive growth of neurobiological research, however, we are rethinking our future as well as uncovering the present. The devastating intellectual and physical decline, which is the hallmark of senile dementia, is seen now as a disease of aging; a pathological deviation from the normal developmental process. Clinical syndromes have been described, structural abnormalities identified, and cellular anomalies uncovered.

The problem of the dementias in the United States is assuming alarming proportions.

Projections from the National Center for Health Statistics indicate that in 1980 about 12% of our population is 65 years or older. Based on northern European estimates of prevalence and incidence of dementia, there are approximately 1 million severely demented and another 3 million moderately to mildly demented persons in the U.S. today. The life expectancy of the severely demented is only one-third to one-half that of their age-matched controls.

At least two-thirds of those with severe senile dementia suffer from Alzheimer's disease. In recent years, many scientists have argued that distinctions between senile dementia and Alzheimer's disease are arbitrary and meaningless. Although senile dementia of the Alzheimer's type (SDAT) and classic Alzheimer's disease, which usually affects people under the age of 65, may well be the same disorder, other forms of senile dementia with differing etiologies give rise to similar appalling symptoms. The spongiform encephalopathies, kuru and Creutzfeldt-Jacob disease, are the consequence of an unusual virus, or "viroid", which has properties unlike most conventional viruses. The span between infection and signs of the illness can be as long as 8 or 10 years. Once apparent, the diseases are characterized by vacuolation and neuronal death, astrocytic proliferation and hypertrophy, axonal and dendritic degeneration in Purkinje cells, and presence of amyloid plaques.

Occlusions of cerebral blood flow, known as multi-infarct dementia, also give rise to a clinical picture identical to that of SDAT. Sophisticated imaging devices, such as the CAT scan, help in making differential diagnoses.

Parkinson's disease dementia has received little attention, but it is a clinical entitity of significance. Since the advent of L-dopa, improved motor control has thrown the cognitive changes in this disorder into bas relief. Parkinsonian dementia may be much more widespread than the special focus of patients on Guam who suffer from amyotrophic lateral sclerosis and Parkinsonian dementia. These patients, as well as other "usual" Parkinson's disease patients, show the neurofibrillary tangles so characteristic of Alzheimer's disease.

The NINCDS will take specific steps in the next few years to increase the level of research effort directed at elucidating the etiology and pathogenesis of these devastating illnesses. The Institute sees as its primary mandate to uncover and describe those factors which produce these disorders and which will lead to the development of new ameliorative treatments and preventive measures.

Structural and Biochemical Studies

The majority of the research supported is aimed at clarifying the structural and biochemical abnormalities which characterize Alzheimer's disease. A number of studies focus on cytoskeletal changes, the neurofibrillary tangles and senile plaques, which are the hallmark of Alzheimer's disease. These tangles appear in the neuronal soma as aggregates of paired helical filaments approximately 200 A in cross section, with a twist approximately 80 A along their length. Both neurofibrillary tangles and their normal, unpaired, and nonhelical neurofilamentary counterparts have been identified as proteins with a molecular weight of around 50,000 daltons.

Other research sponsored by the Institute is aimed at characterizing the biochemical alterations in SDAT. A key feature in these changes are the neuritic or senile plaques, dense masses of extracellular amyloid surrounded by enlarged neurites, mostly axonal boutons containing degenerating mitochondia and lamellar lysomes.

Investigators at Albert Einstein College of Medicine have had a long standing interest in elucidating the structural abnormalities and changes found in Alzheimer's disease brain tissue. One investigator has made the surprising discovery through meticulous cell counts that there is no major decrement of cortical neurons relative to age-matched controls. The acetylcholine muscarinic receptors of the cortex are maintained even though there may be a 75 to 95% loss of cortical choline acetyltranserase (ChAT). Localization of this synthetic enzyme and its receptor is being pursued in human and animal brain tissue by enzyme immunohistochemistry and radiography. Microscopic, histologic and biochemical techniques will be used to compare young and old brains and normal and senile dementia of the Alzheimer's disease type (SDAT) brains.

In other studies, experimentally induced lipofuscin and aluminum induced tangles will be investigated as well as axoplasmic flow in aging animals. Investigators are isolating and characterizing intraneural paired helical filaments, mapping their peptides, binding properties, and antigenic determinants. The biophysical properties of human and porcine neurotubule assembly and disassembly are being explored. Using proteins isolated from the autopsied brains of patients dying with Alzheimer's disease, both young and old, and Guam Parkinsonian dementia, the mechanisms of action of colchicine and vinblastine and the regulatory role of Ca, Mg, and Zn ions on microtubule assembly will be explored.

Understanding of the biology, chemistry and pathology of the fibrous proteins of the nervous system in health and in disease states has been the objective of many NINCDS supported researchers. Several different laboratories are investigating paired helical filaments in the presenile and senile dementias as well as in Down's syndrome. Twisted tubules have been partially purified by investigators at New York University Medical Center. The relationships among various neurofilaments and between these filaments and tublin is being explored. Another investigator at Boston Biomedical Research Institute is characterizing the chemistry and function of neurofilament proteins with regard to their sequencing, immunoreactivity, comparability with other glial fibrillary proteins, and tendency to proliferate in neurons treated by neurolathyrogens.

The role of the microtubules in maintaining cell integrity and function is exceedingly complex; explaining it may be necessary for understanding normative behavior as well as a variety of different disorders, including cancer and the dementias. In Colorado, investigators are looking at clonal cells of the mouse neuroblastoma C1300 that possess high concentrations of tubulin and whose content of microtubule can be directly regulated by growth conditions. The role of microtubule associated proteins in the differentiation will be explored as well as the possibility that these accessory proteins regulate where and when tubulin polymerization occurs with the cell. Work is also continuing on localizing and characterizing GTP binding sites in brain tublin using photo-affinity labeling reagents.

Just as the structures within the cell have sparked interest, the structure which encloses the cell, that elaborate and vital membrane, has attracted the attention of others. Investigators at the University of South Carolina are asking if membrane transport alters with age. As the cell ages, can it still acquire across its membrane from the extracellular fluids the necessary metabolic substrates for energy metabolism and protein synthesis? Do membrane functions in neurotransmission remain the same? Scientists at the University of Missouri have preliminary evidence that some properties of mammalian brain membranes may change with age, and they are in the process of exploring their finding further. In addition to studying the structure, function, and active transport mechanisms of CNS membranes, the role of dietary antioxidants on membranes will be pursued.

The biophysical characteristics of membrane aging is the object of study of investigators at the University of Southern Alabama. Using electron spin resonance techniques, the relationship of monoaminergic systems to cellular changes due to aging will be explored. Two forms of monoamine oxidase with quite distinctive properties, MAO-A and MAO-B, have been identified. These enzymes have been shown to increase markedly in activity in specific regions of aging brains. A study of the MAO-membrane system should contribute to our understanding of the aging process in biological membranes.

The complex interaction of the endocrine system with neurotransmitters and neuromodulators is an area recently coming to the forefront of scientific attention. At the University of Pennsylvania, scientists are looking at the role of neuroendocrine factors in regulating catecholaminergic receptors in the central nervous system. They are seeking to determine if the reduced ability of brain tissue to regulate the density of these receptors may impair neuroendocrine feedback mechanisms. Age related changes may effect the density, function, and adaptive capacity of the cholinergic receptors in the central nervous system. Thus age may work its effects on neurotransmitters through the mediation of the neuroendocrine system. Through in vitro culture studies using the pineal gland from young and old rats, investigators are examining the rate of catecholamine receptor synthesis and turnover, and in particular, how these processes are affected by age.

When animals are given high doses of aluminum, they develop neurofibrillary tangles similar to those seen in Alzheimer's disease. An early report (since contested) claimed that Alzheimer's disease patients also had elevated aluminum levels in their brains. Although this finding is controversial, it did turn attention to the measurement of trace metals in brain tissue of Alzheimer's disease patients. Scientists at the University of Kentucky are looking at a wide spectrum of individuals, from birth to late life, with and without mental impairment, to determine levels of a variety of trace elements. In addition to the highly sophisticated and sensitive radiochemical neutron activation analysis being performed, the investigators have designed new instruments which do not shed metal into their preparations.

The role of the immune system is now being taken into account in studies pursuing the etiology of central nevous system disease. Investigators at Sloan-Kettering Institute for Cancer Research have had a long history of looking at the interface between autoimmunity, immunodeficiency, and central nervous system disorders. Recent data indicates that patients who are IgA deficient absorb foreign proteins through the intestines thus leading to the development of circulating immune complexes. These findings further explain the link between the development of autoimmunity and immunodeficiency in patients. In addition to looking at the effects of dietary intake on autoimmune disease and atherosclerotic cardiovascular disease, investigators are attempting to elucidate immunologic mechanisms in chronic degenerative CNS disorders such as Alzheimer's disease (SDAT). Dietary manipulations will be studied and comprehensive immunologic analyses and lymphocyte characterizations will be made on patients with Down's syndrome and senile dementia.

Animal Models

Animal models of dementia are hard to come by since dementia involves the loss of a capacity we cannot be sure animals ever had. Nonetheless, scientists at the City of Hope in Duarte, California, are studying Drosophila mutants which exhibit both genetically programmed movement disorders and shortened life. They are trying to determine if the shortened life span is also under genetic control, and if so, how the genes produce their effect. Recent data suggest that the thorax of Drosophila may act as an aging center. An intriguing new finding by this laboratory is the isolation of a long-lived mutant. Dubbed "inactive" by its discoverers, the creature can walk, fly, court and mate but prefers to sit around and do nothing. The fly bears witness to the adage that "burning the candle at both ends" is deleterious to one's health, but since this a most pioneering and dedicated laboratory, one hopes that they will soon discover a long-lived mutant in the Picasso-Casals mode.

At the University of Pennsylvania, an investigator is looking at the aging process in cultured neurons. In the process, he is developing culturing techniques for neurons which may benefit research on many different brain disorders.

Mutant mice can be excellent systems for studying degenerative processes. An investigator at Indiana University is studying the Purkinje cell degeneration (PCD) mutant as a model of selective cell loss in the nervous system. One model of aging holds that there is genetically programed cell death which gives rise to the characteristic signs of aging. In the PCD mutant, all Purkinje cells irreversibly degenerate. Preliminary work by the investigator on tissue culture explants of PCD cerebellum indicate that degeneration occurs at post natal day 17. The selective degeneration of a particular cell type allows the researcher to look at neurotransmitter functioning in the cerebellum, focusing on GABA which is a primary neurotransmitter for Purkinje, Basket, and Golgi cells.

The assumption that aging entails cell loss can be meticulously tested as new technologies permit computer assisted graphs and reconstruction methods to enumerate and characterize the nervous system. When specific brain masses have been carefully assessed, several studies have indicated little or no cell loss. But the common wisdom about aging is that it entails programed cell death in the same fashion that early development requires cell death. New technology permits the generation and analysis of quantitative data concerning neuron types and numbers, and measurements of axons and synaptic distributions. An investigator at Children's Hospital Medical Center, Boston is looking at four separate neuronal systems to test the hypothesis that neuronal death is a feature of aging, and that its rate depends on changes in synaptic connections of the neurons at risk. The systems of interest are a) the visual system, b) sciatic nerve, 3) cerebellar cortex, particularly Purkinje cell neurons which are known to decrease in number with age, and 4) cerebellar nuclei, particularly synaptic connections in aging normal mice and mutant mice which loose portions of their axonal input.

Clinical Studies

A large program project on "Senile Dementia: Alzheimer and Vascular Disorders" at Albert Einstein College of Medicine takes an interdisciplinary approach to studying the dementias. Clinicians, biochemists, neuropathologists and neurophysiologists, psychologists, mathematicians and many others turn their talents toward discovering the etiology of these diseases and developing appropriate treatments. Investigators are interested in the nature, incidence, prevalence and course of senile dementias. The identification of risk factors and prevention will receive considerable attention.

The program has three major sections. Section I consists of laboratory studies relating to the etiology and pathogenesis of senile dementia, particularly of the Alzheimer type (SDAT). One project will attempt to grow paired helical filaments in culture. Another explores the possibility that a persistant virus infection may cause SDAT. Two other projects will focus on the localization (through immunocytochemistry) and regional distribution of five peptides in normal and senile human brains and explore the possible relationships of these peptides to the composition of neuritic plaques and tangles.

Section II continues several clinical and psychological studies of SDAT now in progress. A longitudinal study of 500 residents of a nursing home has generated a wealth of biological and psychological data. As residents die, approximately 40 brains a year will be available for correlations of postmortems biochemistry with premortem clinical parameters.

The third section consists of a large prospective study of about 640 people drawn from two nursing facilities and "normal" elderly volunteers drawn from the community. The prospective study will identify risk factors in dementia produced primarily by multiple cerebrovascular infarcts.

The diagnosis of Alzheimer's disease is made on clinical grounds, more as a result of the elimination of other disorders than from specific signs of the disorder itself. Confirmation must await autopsy. At the University of California at Irvine, an investigator is in the process of developing a rapid neuropsychological screening test which, hopefully, will be able to serve as an early screen for dementia. Development of the test will take place in a large, well defined retirement community in Southern California. Laboratory findings and other data will also will also be collected on this sample, making it an excellent prospective study of a very different sample than the Einstein study for the identification of risk factors and possible etiologic clues.

Genetic factors undoubtedly play a complex role in shaping the aging process, but we have much to learn about how they work their influence. Some cases of Alzheimer's disease clearly follow a Mendelian pattern of transmision (dominant) while in other families there seems to be only an increased risk among relatives of a patient. If children with Down's syndrome (Trisomy 21) live long enough, they often develop Alzheimer's disease.

Investigators at the University of Colorado have examined the chromosomes of members of families of Alzheimer's disease patients and have discovered greater aneuploidy than would be expected. They are following these families to determine if aneuploidy may be a preclinical diagnostic sign as well as a possible etiologic clue.

Tardive Dyskinesia

A disorder closely related to Huntington's disease in symptomatology appearing as a result of prolonged neuroleptic treatment is tardive dyskinesia. Unfortunately, no effective treatments have been developed for this disorder as well, but scientists at the Portland, Oregon, Veterans Administration Hospital are trying to determine a subgroup of this population which is responsive the therapy by danol, a possible acetylcholine precursor.

An investigator at the University of Texas is using a cat model to try to produce the drug - induced oral facial dyskinesia of tardive dyskinesia. Based on the hypothesis that these oral facial movements are due to the development of a dopamine receptor hypersensitivity to the presence of dopamine, the investigator is attempting in cats to reproduce hypersensitivity in cranial nerve nuclei which play a crucial role in regulating facial movement.

General Studies

The biochemical, structural, functional characterization of the basal ganglia in general, unrelated to any specific disorder, has been drawing the attention of an increasing number of scientists. At the University of Texas, investigators are trying to understand the GABA receptor in all its complexity. The effects of drugs such as anionic transport inhibitors, anticonvulsants, and psychoactive agents are being explored as well as the possiblity that altered chloride permeability may be a factor in disorders involving altered GABAergic function.

At the University of Maryland, investigators are looking at the potential precursors of gama amino butyric acid to explore alternate pathways for GABA production in the brain. The pharmacological properties of intrinsic caudate neurons in cats are under investigation at the University of South Carolina.

Investigators at the University of Minnesota are turning their investigation to a detailed look at cerebellar anatomy and physiology. Their research program is directed towards an analysis of the effects of proprioceptive and exteroceptive inputs on spinocerebellar systems and on specific regions of cerebellar cortex.

Purkinje cell degeneration mutant mice (PCD) will be compared with granule cell deficient mutants to learn the effects of Purkinje terminal degeneration on target cells in the deep nuclei. If a dense GABA releasing afferent pathway is severed, what is the response of the deep nuclei? The biochemical response to a structural change in a genetic mutant involving the loss of one particular cell type will be studied at Children's

Hospital Medical Center.

Questions of brain asymmetry in response to cerebral damage are being explored by investigators at Mt. Sinai School of Medicine. The neuroanatomical structures involved in producing and maintaining laterality, including the role of the commissural pathways are being identified while investigators also look for neurochemical asymmetries in different brain regions. Rats which demonstrate lateral turning reactions with chemical lesions will be studied to learn further about this rotational response and its relationship to cerebral asymmetry. Differences between spontaneously rotating and non-rotating rats will be identified.

A study at SUNY - Stony Brook looks at interactions between two neuronal systems: the trigeminal input to the basal ganglia is being studied, in particular, the globus pallidus and entopenduncular nucleus. Electrophysiological techniques will be used to examine the effects of the basal ganglia on the organization of oral facial behavior. While investigators at SUNY are looking at the input of one neuronal system on another, investigators at the University of California at Irvine are looking at axonal collateralization from monoamine nerve cells in the CNS. The investigator plans to determine the percent of individual cells within a given nucleus of interest that send axons to different regions of the brain and the percent of cells sending them to the same set of regions. Three particular regions will be examined for their axonal growth into the same or other cortical, limbic, or striatal structures.

A projection log of key areas of collateralization of monoaminergic neurons will be the result of this research. A unique feature of the work is the use of double labelling techniques to see if the same neuron projects to two or more different areas of the CNS.

Future Goals

The wealth of research findings is steadily expanding, but so too are the numbers of victims afflicted by the disorders of aging. Increasing numbers of new investigators must be recruited to this area to maintain and accelerate the momentum of discovery.

NEUROLOGICAL DISORDERS OF EARLY LIFE
INTRODUCTION

This program covers several neurological areas pertaining primarily to the developmental, metabolic and genetic aspects of the developing nervous system. Statistically this program supports 214 research projects including three program projects active as of April, 1980, with an investment of about 16.5 million dollars. In fiscal year 1979, a total number of 175 competing research grant applications were assigned to this program. Of the approved ones, 73 projects were funded giving a funding ratio of about 3:7.

A great many disorders of the developing nervous system are the result of environmental influences on brain development, either *in utero* or in extrauterine life. Even those diseases that have a definite genetically determined pattern of inheritance often vary in the expression of the disease, including the rate of progression and the severity of symptoms. It is quite possible that some of this variability relates to an interrelationship between genetic and environmental determinants of disease. The environment exerts myriad external influences that can modify the organism. The expression of incapacitating genetic disorders already has been altered significantly by changing the environment; in the case of PKU, the patient's diet is altered to decrease the amount of phenylalanine ingested.

The prevention or treatment of developmental disorders of the nervous system depends upon increased understanding of the mechanisms that regulate brain growth and organization, especially those factors which enhance the plasticity of the brain, i.e., its ability to recover structure and function despite an insult, reflecting the true functional reserves of the developing brain. The environment in which the brain develops also exerts serious insults to the organism. However, environmental manipulation may also exert positive effects upon the developing brain. The biochemical basis of brain damage, particularly genetically determined damage, are being studied in order to be better able to identify patients prior to the onset of serious symptoms and to prevent or treat their disease.

All these areas of inquiry imply that a very close interrelationship between basic and applied biomedical and behavioral research will continue. Prior experience suggests that, with few exceptions, important advances in the treatment of developmental diseases have depended upon basic scientific investigations of the anatomy, physiology, and biochemistry of the developing brain and of the effects of well-defined aberrations upon subsequent behavior. Alternatively, many fundamental discoveries concerning the growth and organization of the nervous system have developed from inquiries into genetic and environmental disorders of brain function. The close interdependence of laboratory and clinical sciences is simple anatomical observations to the application of highly sophisticated technology to unravel neurobiological phenomena.

The rest of the report is prepared according to the topics identified by the National Research Strategy Panel for Neurological Developmental Disorders. These topics witn their narratives are given below.

Neurobiology

In this section, emphasis is placed on studies which focus on neuronal genesis and migration; dendritic and axonal development; synaptogenesis; formation of pathways and connections; axonal transport; and studies which foster our understanding of glia and their relationship to neuronal development. Research is conducted on the structures and functions of the various functional systems within the mammalian CNS as well as plasticity and environmental factors. Other studies address the role of teratogens in producing alteration and the ability of the brain to recover. Efforts are made to develop appropriate animal models of developmental disorders.

Several studies are being conducted which make use of cells in tissue culture. For example, they include: study of synaptogenesis and synaptic transmission, role of NGF, microfilaments and microtubules in the formation of axonal processes, effects of specific nutritional deprivations on *in vitro* cell maturation; nuerotransmitter release during development of neuron-to-neuron synapse *in vitro*; growth, development and regeneration of neurons in relation to mechanisms underlying the formation of regionally organized synaptic networks in specific CNS target tissues.

Some projects are devoted to investigations of the role of specific cell surface components on reaggregation, sorting, cell migration, synaptogenesis and neuronal recognition factors in brain histogenesis. Other projects are related to molecular basis of cell recognition and identification during the early developmental stages. Studies are directed to use immunological methods to further define the process of cell-to-cell recognition. Since cell surface phenomena have biochemical bases, a few projects are specifically engaged in biochemistry of lectins, discoidin and pallidin - a cAMP binding protein to compare the structures and properties of receptors for these cell surface agents.

Summarized below are the broad areas of research supported by the Neurological Disorders Program. These processes cover developments of the nervous systems and their responses to intrinsic and extrinsic factors as related to certain developmental disorders, if any. It must be pointed out that there exists a considerable overlap in the areas indicated.

1. Early morphogenesis.

well demonstrated in the investigation of disorders of the developing nervous system supported by this program.

PROGRAM PROJECTS

As alluded to earlier, this program supports three program projects (POls) all of them deal primarily with the fundamental aspects of developmental neurobiology. For example, the project entitled "Ontogenesis of Neurochemistry and Function" deals with the studies to determine the biological consequences of disruption of monoaminergic neurons during their ontogenetic development. Lesions are made in the neurochemically defined monoaminergic nuclei and fiber tracts at various stages of development by surgical or pharmacological means. Long term changes are then looked for by anatomic, histochemical, electrophysiological, behavioral, and neurochemical methods. Comparisons are made with the effects of similar lesions made in adult animals. The experiments are expected to provide information as to whether a critical time period exists during which a particular neurochemical system has a significant effect on the ontogeny of the remaining functional systems of the brain, the nature of the adaptive responses to injury of the neonatal and adult brain, and neuronal plasticity.

The second program project "Neuronal Development, Interaction and Organization" is aimed at understanding the morpho-physiological interrelations of synaptology in a variety of species. Also included are other sub-projects such as the physiology and ultrastructure of rectifying and non-rectifying electronic junctions, biophysics of receptor system for phasic or tonic electronic electrical signals, neural control of feeding behavior, differentiation of Mauthner cells in terms of specificity of synaptic connections, and study of "Meganeurites" in the brain of cats with GMI Gangliosidosis and electrophysiological and anatomical definition of their dendritic fields.

The third program project "Functions and Development of the Synapse" was initiated in this fiscal year with the objectives to: examine the ability of antibodies directed against specific synaptic components to disrupt normal function and development of the neuromuscular junction; identify components of the synaptic basal lamina that are functionally active in directing pre- and/or postsynaptic differentiation at the neuromuscular junction and to study their synthesis; develop improved methods of tissue preparation for direct visualization of macromolecules and of antibodies directed against them at chemical synapses; study the development of cholinergic and peptidergic synapses in sympathetic ganglia; use antibodies to purified synaptic vesicles to study the fate of vesicle proteins during exocytosis and the differentiation of nerve terminals during development; and to use monoclonal antibodies to define synaptic membrane constituents, their distribution at different synapses, and their role in development. The rest of the grant-supported programs in developmental research encompasses areas from

2. Cell proliferation.
3. Cell migration.
4. Dendritic and axonal development.
5. Synaptogenesis and neurotransmission.
6. Energy metabolism.
7. Membrane formation and turnover.
8. Axoplasmic flow.
9. Cell susceptibility to injury and cell death.
10. Plasticity and regeneration.
11. External regulation of brain growth.
12. Development of functional systems.
13. Nerve growth factor.
14. Genetic control of neuronal differentiation and function.
15. Cell surface events.

TIMING OF INSULT

Most of the projects pertaining to the timing of insult are covered under previous sections. These projects follow the development of specific entities or specific systems from the embryonic stage to the pre- and postnatal stages leading to adulthood and in some instances even to senescence. As an example, a comprehensive study of brain development (in the rat) showed that the precise time and site of origin of each neuron class determine the structural and functional organization of the individual neuronal system. The hypothesis is that the precision in the time of origin of neurons within and across brain structures and their connections reflect the importance of chronological factors as determinants of structural and functional organization of the brain. The hope is to obtain an understanding as to what extent neurons are specified at the time of their formations in the germinal neuroepithelium and what influences are exerted on them by the successive waves of neurons or their processes with which they come in contact.

Another example of the time of insult can be cited of the pathological effects of monosodium glutamate, a widely used food additive. This amino acid is cytotoxic to infant when taken orally and produces lesions of the arcuate nucleus of the hypothalmus of the rat and monkey. The thrust of this project centers on the time course of glutamate's action to ascertain if there is a period in the development of the infant (mouse) during which a dose of glutamate is sufficient to destroy arcuate neurons, but yet will fail to produce obesity or harm the endocrine system.

Another project involves pre- and postnatal pharmacological manipulation of central neurotransmitter system during periods of rapid CNS growth and differentiation, and subsequent assessment of the alterations in the maturation of other related transmitter system as well as assessment of permanent influences on central neurochemical activity in adulthood. The project aims to generate important data concerning development of CNS transmitter systems, the interaction of various systems, the ontogenic and permanent consequences of perinatal neurochemical manipulations.

NUTRITION

Studies are underway to clarify morphological features of vitamin E deficiency. In vitamin E deficient animals excessive accumulation of lysophosphatidylcholine and alterations in NADPH-linked enzyme activities have been found. In vitamin E deficient monkeys and humans there has been a demonstration of a "dying-back" of central and peripheral neuropathy. Studies are being conducted to find neuroglial and neuronal factors that are likely to affect glial proliferation and differentiation using as a model hypomyelination in the optic nerve of mutant and malnourished rats. These malnourished animals are used to confirm and extend earlier reports that neonatal malnourished animals can lead to glial abnormalities. Another project is concerned with the effect of essential fatty acids deficiency as well as diet containing only saturated fat or trans fatty acids on lipid metabolism in the brain during the period when it is undergoing its most rapid growth and development.

A few projects are devoted to the study of thiamine and thiamine deficiency. Thiamine deficiency is a classical example of a neurological disorder in which the catabolism of carbohydrates by the brain is impaired. Such disorders, in which the perfusion of the brain is impaired, are a major cause of neurological disability in people of all ages including the elderly. Furthermore, thiamine deficiency is still a major public health problem. In the USA it is seen primarily in people who are severely malnourished secondary to other illnesses--often alcoholics. Although prevention and treatment with thiamine are generally effective, the mechanisms of brain damage in thiamine deficiency and the factors which predispose some malnourished people to becoming thiamine-deficient are not known. The overall objective of these projects is to clarify the mechanisms of brain damage in thiamine deficiency. Specific goals are to measure the synthesis of acetylcholine from glucose and choline and levels of cyclic AMP and cyclic GMP in the brains of rats with various type of thiamine deficiency.

Role of vitamin B_6 in the development of CNS is being investigated. The objectives are to study the effect of vitamin B_6 on the developing central nervous system to learn the relationships between feeding marginal levels of vitamin B_6 to the mother and measurements of cortical thickness, cell packing densities, dendritic elaborations, spine densities and myelination patterns in the central nervous system of the progeny, and if there are relationships between the nervous symptoms in the progeny and the morphology of the central nervous system. A correlative approach is emphasized whereby information from electronmicroscopy and cytochemistry will be combined with nutritional, developmental and other parameters to provide a meaningful morphological framework in which anatomical effects of deficiency of vitamin B_6 can then be evaluated.

Acute salt poisoning in young mice induces hypoglycemia and reduces the brain glucose content. Studies are underway to determine the pathophysiology of this association in muscle and brain by studying glucose uptake and glucose metabolism and comparisons are being made with plasma insulin levels.

A few projects are using tissue culture approach to study the specific nutritional deprivation on in vitro malnutrition. Explant cultures from spinal cord, cerebellum and other parts of the brain are grown in media deficient in various nutrients, such as fatty acids, ketone bodies, hormones, vitamins, glucose etc., and the resulting alterations in the states of myelination and synapse formation are being evaluated. Also investigated are transmitter enzymes and myelin and glial-marker enzymes.

DRUGS AND TOXINS

Projects under this group specifically deal with effects of metals, amino acids or organic acids. Tellurium neuropathy is unique in that it occurs during early myelinogenesis and the neuropathy is self-limiting in that remyelination takes place even with continued tellurium administration. This phenomenon is now being examined. Copper metabolism, especially copper tissue protein is being examined in a mutant mouse model to study human genetic disease. Menke's Kinky Hair Syndrome is a disease in which decreased absorption of copper from the gut has been observed and which ultimately results in a nervous system disorder. Infants develop normally at first, but then failure of psychomotor development occurs with the onset of seizures, spasticity and decerebrate posturing. The hair is sparse and has a wiry texture; when examined under a microscope, it shows twisting of the shafts. Concentrations of copper in serum are quite low and it is claimed that progresstion of the disease can be slowed by parenteral copper therapy. However, it is not certain that this treatment completely corrects the disorder although the concentrations of copper in serum return to normal. Thus one cannot be sure that copper malabsorption and the low concentration of copper in serum are entirely responsible for this neurological syndrome. A lead-induced cerebral microcirculatory injury is being studied and this model is compared with similar symptoms of nutritional encephalomalacia in vitamin E-deficient chicks. Excessive amounts of aluminum may cause a metabolic encephalopathy in children and there is a possible relationship between increases of aluminum in the brain and premature development of neurofibrillary tangles in patients with chronic dementia.

Not only are the metal or metallic compounds neurotoxic, certain amino acids are equally potent agents. For example, monosodium glutamate, a widely used meat tenderizer, is cytotoxic to infants when taken orally and produces lesions of the arcuate nucleus of the hypothalamus. Whether or not there is a specific period in development during which a dose of monosodium glutamate is sufficient to destroy this region is not as yet know. Glutamate and aspartate as well as several analogs of these amino acids are capable of penetrating circumventricular neuronal populations. These are being tested in laboratory animals.

In addition to certain amino acids which are neurotoxins, certain Krebs cycle intermediates have also been found to exert injurious influence. For example, neuropathy associated with thiamine deficiency (Leigh's disease) is attributed to suppression of thiamintriphosphate formation. However, its mechanism of action is not known. It is argued that glyoxylate may be the pivotal point in such thiamine-related disorders. This compound is toxic both directly and after conversion to oxalomalate. This is an example of how endogenous metabolites can exert toxic influences either directly or by affecting some other metabolic pathway.

A common acute encephalopathy of childhood is Reye's syndrome, believed to be caused initially by a viral infection such as chickenpox or influenza B accentuated by superimposition of another virus or of more specific toxins such as aflatoxin, hypoglycin, pesticides and their solvents. Exposure to insecticides, solvents and drugs, without virus, has been identified as a possible primary cause of this syndrome. Several metabolic disturbances have been identified as a result of these exposures to toxins, each of which could result in an acute disturbance of brain function. Reyes' syndrome is then an example of how a metabolic and degenerative disease can occur which, at present, is considered secondary to damage to other organ systems.

HEREDITARY LIPID STORAGE DISEASES AND OTHER METABOLIC DISORDERS

In this section there are over 50 projects, of these about 25 projects are directed towards inherited metabolic disorders. The program supports fundamental as well as clinically applied research on lipid and other inherited diseases. Some of these diseases are Nieman-Pick, Gaucher's, Krabbe's, Fabry's, Metachromatic leukodystrophy, etc. Gangliosidoses (e.g., GMI, GM2, GM3) form an integral part of this research area. Also included in this program are related areas pertaining to myelin, cholesterol, phospholipids, keto and hydroxy fatty acid metabolism.

Although the progress in enzyme replacement therapy has been significant, the optimistic goals of effective therapy for human lysosomal storage diseases have not been realized. There are several hurdles to be surmounted before such a therapy can become a reality. These include: protection of replaced enzyme against bioinactivation and immunological reactivity, perfection of methods for delivery to target sites, availability of natural substrates to test the missing enzymes in vitro, and availability of animal models replicating these diseases for testing therapeutic strategies. Considerable progress in these areas has been made experimentally. However, once an affected child is born with any one of these diseases there is at present very little to offer to restore him to a normal and productive state. Some alternative methods need to be explored. These should include safe and effective means to penetrate the blood brain barrier, delivery of missing enzyme by "encapsulation", use of external agents to activate dominant enzymes which can safely cross the blood brain barrier, production of endogenous stimulators, such as peptides, to complement or replace the missing enzyme, and use of internal or external inhibitors to slow down the enzyme activity which produces the accumulated metabolite. These and other approaches are being exploited.

SPECIFIC PRE- AND POSTNATAL NEUROLOGICAL DEFECTS

Cerebral Palsy - birth injuries: studies are directed to observe alteration in neuronal pathways and connections which develop after specific brain lesions are inflicted in neonatal rats. Another project is developing objective tests of motor performance in patients with cerebral palsy, stroke and spinal cord injury and compares abnormal reflex responses and motor tracking capabilities. Effects of cerebellar stimulation in these patients will be evaluated in respect to these parameters, and other functional measures. Experimental studies are conducted on the effects of controlled hypoxic insults administered to fetal, new born, and adult rats with emphasis on the maturation of the CNS. Another project is engaged in integrating behavioral procedures for assessing motor activity with most promising drug treatment protocols for cerebral palsy and dystonia patients.

Hydrocephalus: A few projects are devoted to the study of hydrocephalus and related aspects. Some investigators are studying the role of choroid plexus in the regulation of CSF formation and absorption, ions (K, Mg, Ca, Cl, etc.) transport from plasma to CSF, effects of various exogenous and endogenous factors which influence and regulate CSF formation and transport in order to understand how the developing brain regulates its electrolytes and acid-base metabolism.

Myelomeningocele: There are 4 projects presently supported by the Neurological Disorders Program dealing with various aspects of Spina Bifida One is to investigate the role of monoamines as "differentiating signals" in the neural tube, the detailed study of interrelation between serotonin neurons and neuroepithelial cells in development, the interactions of steroids and monoamines during neurogenesis, the role of serotonin in neural tube closure and the effects of various treatments on monoamine levels in the developing brain. The second project deals with an in vivo and an in vitro preparation of spinal neurons in which the development of morphological and functional characteristics are being studied. Recently, the development of electrical excitability in Rohon-Beard cells in (tadpole) spinal cord, starting with a stage just prior to closure of the neural tube, has been studied. The results showed that the cells were inexcitable initially but when the action potential first appears, the inward current is carried by Ca++. Later it is carried by Na+ and Ca++, and then only by Na+. Similar changes were found in cells cultured in vitro although it was difficult to identify Rohon-Beard cells by anatomical or physiological cues. These experiments are being extended to study the development of chemosensitivity of these cells in vivo and in vitro. Third project deals with the rehabilitation of myelomeningocele patients and tends to develop and test effective behavioral medicine (biofeedback) training procedures for treating fecal incontinence in these patients, to determine the physiological mechanisms underlying fecal incontinence in this group and the physiological mechanism by which biofeedback training results in the establishment of bowel control of some patients, and to determine whether external and sphincter conditioning will generalize to the external urethral spincter and result in a reduction in urinary incontinence. Fourth project deals with the mechanisms involved in neural tube, early brain, and somite morphogenesis. During neural tube and early brain formation, the neural plate elongates and rolls into a tube and the anterior extention of this tube expands in a disproportionate fashion to the rest of the tube to form a brain. The investigators are examining the forces involved in tube formation and brain expansion. They demonstrated that tubing is an endogenous characteristic of isolated neural plate and is not due to extra-plate tissue or forces. They have examined in detail cell changes associated with plate elongation and tube formation. They have also described accurately cell movements, shape changes, volume changes, and have carefully documented the distortions of the neural plate. From these studies, they have proposed a role for the viscoelastic properties of the neural sheet during elongation which may result in the rolling behavior of the neural tube tissue. Evidence is presented indicating that cerebrospinal fluid pressure is responsible in part for outpocketing of the brain portion of the neural tissue.

Investigations are being conducted to study the mechanisms involved in early neural tissue morphogenesis and map the movement of cells during neural plate formation in the chick. Cell shape changes will be examined during this period and apical regions will be monitored during this time. Careful analysis of the neural plate and tube will permit an assessment of stress areas, shearing forces, and distortion regions. These parameters will be valuable in the development of mechanistic models. Developing embryos will be treated with drugs affecting microtubules, microfilaments, and the cell surface in order to ascertain the involvement of these components in morphogenetic events. Tube formation and early brain development will be monitored by scanning and transmission electron microscopy. The involvement of the notochord in elongation will be assessed by microsurgically removing it and then monitoring subsequent morphogenesis. In addition, plate closure will be examined in embryos prevented from midline elongation by pinning.

Minimal Brain Dysfunction: Minimal brain dysfunction (MBD) is recognized to be one of the most pressing problems in contemporary medical practice affecting an estimated 5-10% of the school population. Clinically the disorder exhibits certain cardinal features which include: onset in early life and evolving clinical picture throughout childhood; involuntary hyperactivity which completely surpasses normal-hyperactivity, however, which disappears or abates as the child approaches adolescence; evidence of impaired cognitive performance; and inability to adjust to changes in the environment.

Of particular interest is the evidence from several lines of investigation which supports the notion that many of the features of the MBD syndrome may be related to brain catecholaminergic mechanisms. Administration of amphetamine, or the closely related stimulant, methylphenidate, to many children with MBD often results in a pronounced decrease in motor activity and improvement in tests of performance. Pharmacologic data suggest that central catecholaminergic systems mediate the actions of amphetamine, and since amphetamines appear to affect the symptoms of MBD, central catecholaminergic systems might be related to the symptoms of MBD.

Recent clinical studies involving the determination of monoamine metabolites in CSF lend support to the belief that central catecholaminergic systems may play a role in MBD. Considerable experimental evidence suggests that the conentration in CSF of 5-hydroxyindole acetic acid (5-HIAA) and homovanillic acid (HVA), the major metabolites of serotonin and dopamine, respectively, reflect the activity of their parent amines in brain. Administration of amphetamine resulted in significant alterations in CSF concentrations of HVA but not 5-HIAA in hyperactive youngsters. This is interpreted as supporting an abnormality in central dopaminergic function in children with hyperkinesis. Utilizing the probenecid loading technique, it was found that HVA in children with MBD was significantly reduced compared to controls, but 5-HIAA was not altered. Thus, these findings like those above, suggest that central dopaminergic (DA) systems play an important role in MBD rather than serotonergic systems.

It was therefore believed that, along with other unknown etiological factors, MBD is caused by the excessive accumulation or production of dopamine in the early stages of development, and if some way could be found either to deplete or interrupt its production by inhibiting the enzymes that produce it, one could develop a rational basis for treatment of hyperactive and dyslexic children. These suggestions, based upon previous observations, prompted the investigators to develop a 6-hydroxydopamine (6OHDA) treated rat-pups model for investigations of MBD. Using these manipulations specific central DA pathways were lesioned in neonatal rats by 6-OHDA, and a number of similarities between the development profile of rat pups depleted of brain dopamine and certain cardinal symptoms in the clinical syndrome of MBD in children have been observed.

The selective reduction of brain dopamine produced by the intracisternal administration of 6-OHDA to 5 day old rat pups results in a developmental pattern that has many parallels with the clinical syndrome of MBD observed in children. Rat pups treated with 6-OHDA as neonates are significantly more active than their littermate controls during the period of behavioral arousal that occurs between two-three weeks of age. However, as the rat pups approach maturity the hyperactivity initially observed in the 6-OHDA treated animals is no longer apparent. This finding appears to correspond to that found in children with the clinical syndrome of MBD. In these affected youngsters hyperactivity is pronounced until 10-12 years of age, but then abates, and is similar to that seen in the experimental model of hyperactivity in rats. Furthermore, in children with MBD, although the hyperactivity does disappear, associated cognitive difficulties frequently persist. Similarly, rat pups depleted of brain dopamine as neonates have in addition, deficits in learning, as demonstrated by the persistently impaired performance in both the T-maze and shuttle box avoidance tasks. As noted above, administration of stimulant medications such as amphetamine or methylphenidate to children with MBD frequently results in a diminution of hyperactivity. Rat pups depleted of brain dopamine respond in a similar fashion with attenuation of activity levels and significant improvement of avoidance performance. Still another parallel may be found in the response of both children with MBD and 6-OHDA treated rat pups to a sudden alteration in the environment. For a child with MBD, any change in milieu all too often results in an exacerbation of both hyperactivity and distractibility. This inability to adjust well to change has its counterpart in the impaired ability of 6-OHDA treated rat pups to modulate their activity when placed in a new environment; an effect described experimentally as habituation of activity.

In the future specific central DA pathways will be lesioned in neonatal rats by 6-OHDA. The accuracy, magnitude, and specificity of the destruction of cell bodies in the nigrostriatal and mesolimbic systems will be determined by chemical analysis of DA levels in the striatum, nucleus accumbens, and olfactory tubercle. Behavioral measurements, following 6-OHDA treatment will be correlated with residual concentrations of DA, NE, HVA, catechol-O-methyl transferase, and catecholamine turnover. Among the brain areas to be studied are the hypothalamus, hippocampus, pons, and medulla. Some of the behavioral activities will be monitored and compared with those of the control animals.

Attempts will be made to reverse some of these behavioral anomalies by using medication commonly employed in treating MBD, namely amphetamine and methylphenidate together with other drugs such as apomorphine (a DA agonist), haloperidol (DA antagonist), bromocryptine (agonist), and clonidine (NE agonist).

Reye's Syndrome (RS): Reye's Syndrome is a sudden and fulminant disease of childhood characterized by hyperammonemia, encephalopathy and massive fatty infiltration of the viscera, especially the liver. Characteristically, the disease is preceded by a prodromal viral infection, of a few days duration, which is most often influenza B or varicella. Recovery from the prodrome is usually followed by onset of intractable vomiting, hepatomegaly and signs of rapidly progressive cerebral edema. In approximately 40 per cent of cases, the encephalopathy proceeds to the extent of irreversible brain stem damage and even death, often within 24-48 hours from onset of the acute phase of this disease. However, in areas where special treatment teams are available, mortality rates have been reduced to approximately 20%. The Center for Disease Control (CDC) has estimated that Reye's syndrome has become the leading cause of virus-associated central nervous system disease in individuals from 0 to 24 years old. Epidemiological studies at the CDC have demonstrated that the disease in the United States appears to be concentrated in a southwest to northeast band which includes New York State.

Etiology: Most authorities agree that a non-specific virus is involved in the prodromal phase of the disease. Superimposition of another more specific virus or of more specific toxins such as aflatoxin, hypoglycin or insecticides (and their solvents) have been suggested as complicating and/or contributing factors. Inborn errors of metabolism have also been mentioned as a possibility predisposing to this disease. Accidental poisonings by the agents mentioned can never be completely eliminated. From a consideration of these possible etiologic conditions leading to the Reye's Syndrome, one must conclude that viable, post-insult therapy will continue to be needed until satisfactory management of such patients is attained. The greatest chance for successful prophylactic control of this disease lies in the possibility that an environmental influence or toxin might be implicated, identified and eliminated. However, the highly sporadic nature of the disease is often offered as an argument against this possibility. If environmental manipulations are not the key to prevention and no secondary infectious agent can be isolated, one is left with the requirement for an effective treatment as essential to the control of this disease.

Pathology: The clinical course of RS begins with intractable vomiting and lethargy, and proceeds through rapid deterioration of neurological function. Patients with RS usually have high concentrations of serum ammonia, high serum transaminase activity, and prolonged prothrombin times which originally suggested a hepatic basis for the encephalopathy. However, more recent evidence suggests that impaired liver function alone may not be the primary basis for the illness. In some cases, the CNS symptoms precede evidence of hepatic involvement. High serum concentrations of creatinine phosphokinase indicate that muscle may be affected. Fatty degeneration occurs in several of the viscera, not just liver. Morphological examination of biopsies from RS patients have shown structural alterations in mitochondria from liver, brain, and skeletal muscle. The suggestion that an accumulating metabolite or an exogenous toxin may be causing cellular damage has been made repeatedly.

Animal Model and Biochemical Correlates: Fatty acid metabolism: High values of circulating blood ammonia are characteristic of the acute phase of Reye's Syndrome. The hyperammonemia may be secondary to a fatty acidemia, possibly as a consequence of disruption of hepatic mitochondrial metabolism and associated urea cycle activity. Some of the published etiologic models, for example, animopentenoic acid intoxication, have led to simultaneous elevation of serum free fatty acids and ammonia. The latter two substances may act synergistically in the induction of experimental coma.

Clinical findings on the levels of serum free fatty acids in children with Rey's Syndrome indicated increased levels (up to 30 fold) of long chain fatty acids in acute phase sera from such patients. A biochemical manipulation is being sought to deal therapeutically with this elevation of free fatty acids. In order to explore such a rationale, the intoxication of rats with fatty acids was examined. Because of the experimental difficulties in solubilization and absorption of long chain fatty acids, a short chain fatty acid (SCFA), sodium octanoate, was used in a rat model.

With these manipulations, results from this pilot study indicated that the coma inducing effects of sodium octanoate could be modified or eliminated by the concomitant or subsequent injection of D, L-carnitine. Rats given sodium octanoate remained unconscious as measured by absence of the righting reflex for approximately 35 minutes. Injection of D, L-carnitine one minute after the onset of coma reduced the period of unconsciousness by approximately 50 per cent. A simultaneous injection of carnitine either substantially reduced or prevented the period of coma.

Carnitine was chosen as potential therapeutic agent for octanoate-induced toxicity because it is known to promote the metabolism of various fatty acids by enhancing transport of such compounds across the mitochondrial membrane. Such enhancement of fatty acid transport is more effective for long chain fatty acids than short chain fatty acids, the SCFA possessing the ability to traverse the mitochondrial membrane by simple diffusion. Carnitine also reverses the effects of hypoglycin analogs in rats, and has also been reported to effectively antagonize acute alcohol-induced triglyceride accumulation in rat liver. Rats on a diet devoid of carnitine or its metabolic precursor, lysine, develop fatty infiltration of the liver. The report of elevated plasma levels of lysine in children with Reye's Syndrome suggests a possible defect in carnitine synthesis. All of these findings supported choice of carnitine as a possible antagonist to octanoate toxicity. In addition to the anticipated effects of carnitine on fatty acid metabolism, it is postulated that carnitine might also be of use in interrupting positive feedback loops that might be present if the fatty acidemia was secondary to other blood derangements. Thus, a sequence of a) urea cycle derangement, b) increased blood ammonia, c) fatty acidemia, d) hepatocellular fatty acid infiltration, and e) mitochondrial damage, all of which would lead to further urea cycle derangement, might possibly be interrupted if the fatty acids could be rapidly cleared by hepatic tissue. These and other possibilities can be examined with the establishment of the animal model based on such a hypothetical pathogenesis.

Mitochondrial Impairment and Serum Factor: Morphological examination of biopsies from RS patients have shown structural alterations in mitochondria from liver, brain and skeletel muscle. On the basis of these observations it was decided to investigate the hypothesis that a "serum factor" may be responsible for the mitochondrial damage seen in RS. Rat liver mitochondria were isolated and assessed for classical parameters of respiratory function in vitro in the presence or absence of RS serum. Using this general approach it was possible to demonstrate an inhibitory effect of RS serum on the oxidative metabolism of isolated rat liver mitochondria. Serum from normal donors or from comatose patients with chronic cirrhosis, autoimmune disease (lupus erythematosus), or with chronic active liver disease (microcystic) had no effect on mitochondrial function. Also serum from RS patients after "total body washout" or exchange transfusion or both did not change mitochondrial functions. The results suggested the existence of a serum factor which might be important in the pathogenesis of RS. Further studies investigate the hypothesis that the putative serum factor is important in the pathogenesis of RS serum affecting energy-linked functions such as cellular respiration, fatty acid oxidation, urea synthesis, protein synthesis, and glycolysis. An attempt will be made to define the chemical identity of this factor and the potential usefulness of the biochemical assays as a diagnostic test for the presence of RS factor will be explored.

Monoamines and Reye's Syndrome: Evidence from several lines of investigation suggests that brain edema plays a vital role in RS. Numerous reports have emphasized that brain weight is increased. At autopsy, the cortical gyri are flattened, the ventricles are decreased in size, and tonsillar coning is present, suggesting brain edema. On clinical grounds, cerebrospinal fluid pressure is frequently increased, particularly in children who subsequently die. Despite this compelling evidence of brain edema in RS, little is known of the mechanisms involved. Continuous intraventricular monitoring in the management of Reye's Syndrome provided the opportunity to define some of the factors influencing the development of brain edema. In particular the concentrations of the metabolites of serotonin (5-hydroxyindoleacetic acid, 5-HIAA) and dopamine (homovanillic acid, HVA) in the ventricular fluid were examined. A markedly increased concentration of homovanillic acid during the early period of brain edema in RS was found. The elevated concentrations of HVA in children with RS supports the idea that brain monoaminergic systems may be involved in the genesis of this disorder. The results suggested that cerebral dopamine, rather than serotonergic, mechanisms are most important, since 5-HIAA was unchanged. It is possible that an undefined metabolic insult may initiate cerebral ischemia. Restriction of oxygen supply may induce brain edema. Another consequence may be the release of vasoactive amines into the brain, acting locally to constrict cerebral vessels and exacerbating the damage. If therapeutic measures interrupt this sequence, it may be possible to ameliorate some of the consequences. Therapy might include pharmacologic agents that prevent release of amines or block their actions on receptors. Whether such medication would affect the course of Reye's Syndrome remains to be investigated.

Neuropsychological Consequences of Reye's Syndrome: With increased number of children recovering from the acute encephalopathy of Reye's Syndrome, the need for more information on the neuropsychological sequelae from the disorder becomes urgent. Available data concerning other CNS disorders suggest that a range of disabilities might be anticipated. Over one hundred patients recovering from Reye's Syndrome have been examined. Preliminary findings suggest a highly variable outcome in that IQs ranged from less than 50 to over 100 in moderate to severe cases. Measured IQ scores are not sufficient for indicating the extent of damage resulting from conditions affecting the central nervous system. Therefore, the necessity for using a wider range of more sensitive cognitive, language, and perceptual-motor measures in assessing outcome of treatment is apparent.

Future studies are directed to establish the level and types of neuropsychological deficits immediately following the acute phase of illness. Efforts will be made to determine the relationship between diagnostic laboratory findings, clinical or neurological findings, and the rate and pattern of recovery in neurological findings, and the rate and pattern of recovery in neuropsychological functions, i.e., cognitive, language, perceptual-motor and motor functions by follow-up evaluations at 12 months and 24 months. Parents' understanding of the etiology, prognosis, and sequelae of the syndrome as well as their perception of the impact on the family immediately, and at follow-up will be assessed. The nature and priority of rehabilitative needs will be identified as perceived by the family and, when possible, by the patient.

Treatment: Early recognition and the prompt initiation of treatment is important: Treatment consists of general supportive care, along with the appropriate treatment of metabolic imbalance, cerebral edema, and the other problems associated with the disease.

ANNUAL REPORT

October 1, 1979 through September 30, 1980

Epilepsy Branch, NDP

National Institute of Neurological and Communicative Disorders and Stroke

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October 1, 1979--September 30, 1980

Epilepsy Branch
Neurological Disorders Program
National Institute of Neurological and Communicative Disorders and Stroke
National Institutes of Health

Roger J. Porter, M.D. was appointed Chief, Epilepsy Branch effective March 1, 1980, after serving a period as Acting Chief; this was a stabilizing influence on Branch activities. There were several other notable personnel actions during the year: Barrett Scoville, M.D. was appointed Special Expert in Drug Development in October 1979. Dr. Scoville brings expertise in internal medicine, psychiatry, and drug development and regulation to the Branch. He has already demonstrated high performance and skills which will aid our communication with the pharmaceutical industry and contractors providing data upon which drug development decisions are made. William H. Pitlick, Ph.D. was appointed Health Scientist Administrator with responsibility for the grant administration in the area of epilepsy and other convulsive disorders. He will also aid the Branch's program planning efforts to utilize suggested research directions provided by the Commission for the Control of Epilepsy and Its Consequences, the Panel on Neuromuscular and Convulsive Disorders, and suggestions made by the NIH Epilepsy Advisory Committee. Billy G. White, Head of the Branch's Computing and Statistics group was awarded the Ph.D. degree by Johns Hopkins University in May 1980. The degree followed many years of diligent study coinciding with high productivity during working hours. Judith Lim-Sharpe joined the staff as technical information specialist, and supervises many aspects of the epilepsy information program. The first WHO Neurosciences Fellow at NIH is assigned to the Epilepsy Branch: A. 'Kunle Bademosi, M.D. is a Nigerian specialist in internal medicine with an interest in epilepsy. He is devoting his period of work at NIH to developing an understanding of the pharmacokinetic principles of antiepileptic drug therapy.

The principal effort of the Epilepsy Branch is new drug development. This program consists of individuals who submit new compounds for screening for anticonvulsant activity in rodents, toxicity evaluation with 90-day tests in rats and dogs; evaluation of promising compounds to determine their pharmacokinetic properties and efficacy and side effects in the primate; and controlled clinical trials of new drugs in man. Medicinal chemists in universities and the pharmaceutical industry continue to supply new chemicals for evaluation. The screening project has been developed into a 7-phase test where compounds with high performance are evaluated to determine their anticonvulsant potential. Compounds successfully completing the 7 phases are then considered for rat and/or dog toxicity evaluation. Three compounds have been scheduled for this evaluation, which will be conducted under the terms of a new research contract awarded in March 1980. At its May 1980 meeting, the Subcommittee on Anticonvulsant Drugs reviewed data on 8 additional compounds and suggested a priority order for their toxicity evaluation. Negotiation is now underway with the sponsors of these compounds to determine their willingness to continue participation towards eventual marketing of a new drug. The Subcommittee also reviewed the pharmacologic information and clinical data available on 6 European drugs to determine which would be an acceptable candidate for an NINCDS-sponsored clinical trial in the United States. A French drug, progabide, was selected as the leading candidate and discussions are now underway with the sponsor of the drug regarding a clinical trial. Also, the Branch plans to initiate a Request for Proposals for a controlled clinical trial in complex partial seizures early in the next fiscal year. This would coincide with the availability of a drug for clinical trial. The Branch also provides informal consultation with an American firm regarding their plans for development of a new antiepileptic drug. Informal discussions have also been held with 8 other American firms regarding drugs in various preliminary stages of development. Branch personnel concerned with the drug development program provided a detailed description of the program to the Institute Director and Deputy Director; this review was well received and provides the basis for continued intense activity in this area. Antiepileptic drug development is a concern throughout the world: Two of the 4 topics of the 12th Epilepsy International Symposium held in Copenhagen, Denmark, in September 1980, were devoted to this field--preclinical drug development and controlled trials on antiepileptic drugs were especially relevant themes. The other two themes were differential diagnosis of epileptic seizures and education of the patient and the public. In connection with its drug development program, a number of the Epilepsy Branch staff concerned with drug development participated in this meeting and presented several papers to the more than 900 participants.

Informal liaison and cooperation with the Food and Drug Administration is important to the drug development program. An informal close working relationship exists between personnel of the Division of Neuropharmacological Drug Products, Bureau of Drugs, and the Epilepsy Branch. Staff from the Branch were invited to participate in the FDA's Advisory Committee meeting to recommend changes in the FDA's guidelines for the clinical evaluation of anticonvulsant drugs, to discuss the carcinogenicity of phenytoin, and the design of clinical trials. While at some echelons of the Food and Drug Administration crossover clinical trial designs are regarded as unsatisfactory, certain classes of drugs, among them antiepileptic drugs, are believed to be appropriate for this study design. The Branch staff conducted a comprehensive review of clinical trials conducted for antiepileptic drugs and showed crossover studies were effective and appropriate for this class.

Comprehensive Epilepsy Programs supported by research contract funding have been an important part of the Branch activities for 5 years. Five programs were supported in this manner; the first 3 will end this fiscal year and the remaining 2, next. Because of the impact these programs have had on clinical research, the investigators have made grant applications for continued support through that mechanism. One of the 3, the University of Minnesota, has already been funded by grant. Two others have applied and the final two will also be considered for funding under the grant mechanism. In response to a recommendation from the Commission for the Control of Epilepsy and Its Consequences and the Epilepsy Advisory Committee, the Institute undertook the Request for Proposals for a Comprehensive Epilepsy Program in an urban setting with a minority population. Three proposals were received and carefully reviewed by a Technical Merit Review committee. An award was made in June 1980 to the University of California at Los Angeles for this research.

The Epilepsy Foundation of America and the American Epilepsy Society have agreed to sponsor an international epilepsy symposium to be held in Washington, D.C. in 1983. The NINCDS will cooperate in this symposium. Branch personnel will be deeply involved with its planning, organization, and conduct. Much work has already been done in the planning for the organization, scientific, and local arrangement committees. A selection of a conference service firm to handle the secretarial duties will soon be made. Branch staff will undoubtedly participate even more intensively in the coming year.

A World Health Organization study of the comparative metabolism of phenytoin in varying world populations has been discussed for several years. During the year, substantial progress has been made to develop a protocol for the study and obtain the special stable labelled phenytoin injection to be used in the study. An investigational New Drug Application was filed with the Food and Drug Administration so that a pilot study could be undertaken at the NIH Clinical Center.

Information programs have been important to the Epilepsy Branch from its inception. The Branch continues to provide modest support for Epilepsy Abstracts, makes EPILEPSYLINE available to MEDLINE users through the National Library of Medicine, and prepares specialized bibliographies. The information program was reviewed in depth by an ad hoc group of information specialists and highly endorsed. Consequently, the program will continue to provide the services to the Branch personnel and individuals outside NIH. An alternate source for EPILEPSYLINE than the National Library of Medicine is being investigated and means of strengthening Epilepsy Abstracts are under consideration. Dr. Porter spoke on epilepsy to a large assembly of interested lay persons as one of the NIH series -- Medicine For The Layman. The audience found the talk interesting and enlightening; it will be published in booklet form.

The Branch provided technical facilities for a workshop on aggressive behavior and epilepsy in March 1980. The workshop, sponsored by the Epilepsy Foundation of America, provided the opportunity to view video recordings of "aggressive" behavior occurring during a seizure; investigators from Japan, Europe, and the United States came and participated. The group concluded that such behavior during a seizure occurs extremely rarely, and when it does, it is virtually never directed by the patient for the purpose of bodily harm. In one exceptional case, the aggressive behavior was easily controlled by gentle restraint.

As a consequence of suggestions made by the Commission For the Control of Epilepsy and Its Consequences, NINCDS grant funded conferences were held on Genetics and Epilepsy in Minnesota in July 1980. Another workshop on status epilepticus will be supported by grant. This will be held in San Diego in November 1980.

A number of national and international visitors came to the Epilepsy Branch during the year. It is always a pleasure to discuss our areas of interest with colleagues and exchange ideas and concepts with them.

Dr. Porter continued to serve as Acting Chief, Clinical Epilepsy Section, Experimental Therapeutics Branch, Intramural Research Program, NINCDS during the year as the intramural program seeks a permanent individual for this position. Susumu Sato, M.D. served as Acting Chief, Clinical Neurosciences Branch, Intramural Research Program following the retirement of the former Chief.

Epilepsy is the second-most commonly occurring neurological disorder in the United States. Most estimates indicate the prevalence to be at least one person out of every 100 or more than 2 million people. In addition, 4-5 million people have experienced febrile seizures as children. Many epileptic subjects are well-controlled due in large part to successful therapy with antiepileptic drugs and are able to lead normal lives. However, it is estimated that 400,000-500,000 patients have recurrent, uncontrolled seizures. The physical and psychological consequences of uncontrolled seizures are devastating with marked decreases in life span and a high incidence of suicide in poorly controlled epileptic patients.

Epilepsy is a disorder resulting from abnormal excessive electrical discharges from one or more locations in the brain, which spread over normal or abnormal neuronal pathways. The development of an epileptic focus may arise following a wide variety of events, including fever, trauma, infection, anoxia, or tumors; in many patients, there is no apparent etiology. The location of the focus will determine the nature of seizures and type of behavior associated with the seizure.

Advancement continues in several laboratories in the establishment of seizures in animal models, generation of cell cultures, and isolation of cell components, enabling wide-ranging studies on the nature and control of the spread of abnormal discharges. Human studies are concerned with enhancing diagnostic techniques, evaluation of seizure types, pharmacological intervention and care and management of the epileptic patient.

In FY80, the NDP received 95 applications for research support in convulsive and related paroxysmal disorders, of which 56 were approved and 21 funded, for a total of $2,107,878. Of the funded applications, 13 were new or supplemental awards for $625,673 and 8 were competing renewals for $1,482,205. There are currently 95 active grants totalling $8,121,727.

It is well-known that seizures may be precipitated by a number of events. Several studies are investigating the pathophysiology of epileptogenesis. In rat hippocampal slices, it has been shown that pyramidal cells develop long lasting supersensitivity to acetylcholine following a kindling-induced afterdischarge. This suggests that synaptic modulation may be related to the increased neuronal excitability basic to the epileptic process. Other studies have shown major alterations in the concentration of cholesterol esters in the brain preceding the onset of cobalt-induced seizures. In addition, treatment of neonatal rats with an inhibitor of cholesterol synthesis results in the development of chronic epileptiform activity as evidenced by EEG changes later in life. Similarly, oxygen under high pressure results in a change in lipid peroxidation in the brain cortex which appears to correlate with convulsive activity. Another study has shown that brain cells become seizure-prone when methyl-group donor flux is altered. These and other similar studies will shed light on the processes responsible for abnormal neuronal discharges.

The biochemical events that accompany a seizure are the object of other studies. One such study is defining the roles of cyclic AMP and GMP in cellular depolarization and seizure discharges. Phenytoin, carbamazepine, phenobarbital, primidone, phensuximide, and high concentrations of clonazepam inhibit veratridine-induced accumulation of both cyclic AMP and cyclic GMP. In contrast, ethosuximide, trimethadione, valproic acid, and low concentrations of clonazepam are ineffective or inhibit accumulation of only cyclic GMP. Results suggest that inhibition of cyclic AMP and cyclic GMP accumulation in depolarized brain tissue is a molecular neuropharmacological action characteristic of antiepileptic drugs that have direct effects on cellular membrane function and electroshock seizures. Other results indicate that seizures augment release of catecholamines and adenosine from intracellular stores, and the action of these and other substances causes accumulation of cyclic AMP in epileptic brain. In contrast, cyclic GMP accumulates in epileptic brain as a result of a different presently undefined mechanism. These data further substantiate the hypothesis that cyclic nucleotides have important roles in epilepsy, and may explain some basic mechanisms of seizures and antiepileptic drug actions. Another study is investigating changes in protein synthesis associated with increased cerebral excitability in the kindling phenomenon. It has been shown that phenytoin in therapeutic concentrations inhibits the calcium-dependent phosphorylation of particular brain proteins. The prolonged anticonvulsant action of taurine and GABA are being examined by determining changes in free amino acid content in certain areas of the brain. Tissue cultures of GABA neurons with formation of inhibitory and excitatory synapses have been prepared which allow study of the physiological effect of GABA. Other studies are focusing on the uptake, storage, release, and metabolism of GABA. Preliminary studies indicate fractionation of peripheral nerve into several cellular components is possible in addition to establishing cultures of Schwann cells and cortical neurons. The biochemistry of the central nervous system under various conditions designed to produce systemic ketosis is being investigated in an effort to understand the relationship between ketones, intracellular control mechanism of glucose, and the antiepileptic effect of ketosis. In particular a study focusing on ketogenesis and cerebral glucose utilization has shown that an increase in energy reserves in the brain is caused by ACTH and glucocorticoids, resulting in increased cerebral ATP production. This suggests a possible mechanism for the clinical usefulness of ACTH in neurological disorders.

Cellular physiology in normal as well as abnormal neurological conditions is of great interest to a large number of investigators. Particular attention is being paid to the role of calcium ion in seizure generation caused by penicillin. It has been shown that penicillin blocks the effect of GABA and is associated with an instability of the presynaptic membrane resulting in seizure generation. This instability is accompanied by a large decrease in input resistance of the membrane. Other studies are investigating the relationship between adaptation and ion flux. In Aplysia ganglia it has been found that adaptation proceeds in two phases. The first phase is a rapid decrease in firing lasting 10 seconds. The second, longer phase is produced by a slowly increasing outward current carried by potassium ions. Phenytoin enhances the inward current responsible for the rapid firing of the first phase. The late phase is regulated by free calcium. This finding was also demonstrated in another study which showed the presence of a calcium-dependent K current which terminates the burst in these neurons in a manner similar to that which occurs in the Aplysia cells. Other studies are considering the influence of increased levels of intracellular calcium on synaptic facilitation. The depolarization produced by GABA appears to trigger a voltage-dependent calcium current which further depolarizes the cell. Additional studies are aimed at documenting cerebral metabolism, biochemical changes, and blood flow during seizures.

The further study and development of adequate animal models for the study of epilepsy continues. One model of particular interest is the immunoneurological model which provides a clearly defined target for studying molecular mechanisms. Recurrent seizure activity can be produced in rats and rabbits by injection of antiserum to synaptic membrane of brain gangliosides. Models have been developed for simulation of the phenomenon of "bursting" neurons in molluscan abdominal ganglion. Other studies are examining the effects of diet on the development of aluminum-induced epileptogenic foci in guinea pigs.

Seizures in many patients may be adequately controlled with medical therapy. However, in spite of decades of research, completely effective yet non-toxic antiepileptic drugs have not been found. To this end, the Epilepsy Branch is actively seeking to add to the pharmacological armamentaria of physicians who treat epilepsy. In FY80, 14 grants were awarded to synthesize new compounds for testing in the Drug Development Program. Compounds similar in structure to known anticonvulsants such as quinazolinones, oxopyrimidines, succinimides and benzodiazepines have already been synthesized. Several new classes of compounds are being considered for further development and testing. Already, a series of derivatives of cannabinoids have been synthesized and are currently being evaluated for anticonvulsant effects in rats and rabbits. In addition analogs and derivatives of apomorphine and aminoisoquinoline have been synthesized. Another study is aimed at synthesis of indole-related derivatives, similar in activity to the benzodiazepines. Further development of existing compounds continues. An N-alkylation procedure will produce several N-alkyl-substituted derivations of hydantoins, barbiturates, cinnamic acid derivatives and pyrazolodiazepines. In addition a series of novel sultams and lactams are being synthesized. A variety of compounds are being synthesized with structures based on the suspected involvement of GABA in some forms of epilepsy. This search for GABA-like agents or GABA-transaminase inhibitors offers significant promise in leading to useful agents. Another promising approach is the synthesis of drug and biological constituents such as cholesterol into complexes which would be incorporated semi-permanently into biological membranes. The stereochemistry of a number of existing anticonvulsants is being studied. It has been shown for example, that hydroxycarbamazepine has a similar conformation to phenytoin. In addition, the spatial conformation of other new compounds such as cannabidols are being compared to existing anticonvulsants.

In the meantime, the pharmacological activity of presently known antiepileptics is being intensively investigated at a number of levels. The effects of both anticonvulsant and convulsant drugs on GABA is being studied in nerve cell cultures. These investigations have suggested that postsynaptic modulation of GABA responses may underlie the basic mechanism of action of some antiepileptic drugs. One investigator looking at the effect of GABA and phenytoin suggests that phenytoin prolongs the open time of GABA-operated channels, rather than producing a partial blockage. Another study has shown that barbiturates may block synaptic ion channels. Other results have shown that the amplitude of the hyperpolarizing synaptic potential was greatly diminished by phenobarbital at concentrations which had no effect on pre- or postsynaptic potential.

Pharmacokinetic studies continue to elucidate the time course of absorption, distribution, metabolism and excretion of new as well as established antiepileptic drugs. Studies in normal volunteers receiving intravenous primidone found one-half the dose was excreted intact with a half-life of 6 hours, one-sixth of the dose was converted to phenobarbital with a half-life of 76 hours and one-third was converted to PEMA with a half-life of 16 hours. In chronically medicated patients, blood and urine levels were no different than in the normal volunteers. Other studies are considering the fate of phenobarbital and its major metabolites, including distribution into tissues. Species differences are also being investigated.

More powerful analytical techniques have been developed for quantitation of carbamazepine, primidone, phenobarbital and several metabolites of the above compounds. Given that many currently available drugs are partially effective, the goal of these studies is to optimize therapy for the individual patient using scientific rather than empirical approaches.

Non-pharmacological control of epilepsy continues to be studied. In two studies, operant conditioning of the EEG activity has been shown in some patients to lead to a reduction in seizure rate. Monkeys have been operantly trained to control physiologically identified single neurons in precentral cortex in an attempt to develop a tool for investigating the CNS in an undrugged animal. Work continues on the development of a prosthesis for assisting patients with absence seizures by utilization of feedback techniques. The effects of diet and hormones on the severity and frequency of seizure episodes are being studied.

The sequelae of seizures and their treatment may be devastating both physically and socially. Several investigations are concerned with different levels of the effects of seizure activity. For example, it has been found that during a seizure, the mitochondrial redox state becomes oxidized, due in large part to an increase in ammonia tissue content. This suggests that the seizure has caused a significant change in serine flux, as well as trans-sulfuration and one-carbon metabolism. A fall in levels of N-acetyl-L-aspartate has also been demonstrated during a seizure. These studies were conducted to learn more of the metabolic and biochemical mechanisms and consequences of seizures. Others have shown changes in brain protein synthesis during seizures associated with an increase in the ratio of GDP to GTP. On another level, the relative safety and side effects of phenobarbital and sodium valproate are being evaluated in children. The study is focusing on behavioral and neuropsychological function of the child.

Improved diagnosis and classification of seizure type is the goal of several research projects related to EEG analysis and computerization as well as studies on visual, auditory, and somatosensory evoked potentials.

Support continues for five program projects for epilepsy research, with numerous studies directed at the causes and improved treatment of seizures.

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1979--September 30, 1980

NEW CASTLE STATE HOSPITAL (N01-NS-8-1310)

Title: Development of a Model for Assessment of New Anticonvulsant Agents

Contractor's Project Director: John Van Meter (Acting)

Current Annual Level: $4,000

Objectives: To further develop models to study the efficacy, safety and bioavailability of new antiepileptic drugs in humans. The most recent investigation included study of the antiepileptic property of valproic acid when substituted for phenobarbital in the therapy of patients with generalized seizures refractory to treatment, the evaluation of possible side effects of the drug, and evaluation of drug serum concentrations.

Course of Contract: The study of valproic acid was completed in the fall of 1977. Clinical data was sent to the Epilepsy Branch, NINCDS, Bethesda, for review and preparation for computer aided analysis. Final verification and analysis of the data is underway.

Major Findings: Preliminary analysis of data appears to indicate that sodium valproate may be substituted for phenobarbital in the therapy of patients with generalized seizures.

Significance to NINCDS Program and Biomedical Research: The pharmaceutical industry had demonstrated little interest in developing new antiepileptic agents. Aside from the economic factors involved, one of the industry's major problems is to obtain satisfactory clinical studies of antiepileptic drugs. Through this contract and others, NINCDS has supported clinical studies of antiepileptic drugs. Well controlled studies--as conducted at New Castle State Hospital--will be significant indicators of therapeutic merit of new antiepileptic drugs and may encourage the pharmaceutical industry to develop promising agents for clinical trial. It is anticipated NINCDS-sponsored studies will enable drugs to reach the market more readily, and thus be available to physicians who treat patients with seizures.

Proposed Course of Contract: This contract expired July 15, 1980.

Publications: None

C.T. No. 0700761

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1979--September 30, 1980

UNIVERSITY OF VIRGINIA SCHOOL OF MEDICINE (N01-NS-9-2196)

Title: Absence Seizure Drug Studies

Contractor's Project Director: Fritz E. Dreifuss, M.D.

Current Annual Level: -0-

Objectives: To evaluate the effectiveness of valproic acid and of ethosuximide on the frequency and intensity of absence (petit mal) seizures in patients previously untreated for this disease, and in patients who have failed to be controlled by ethosuximide; to evaluate drug effects on physiologic and other functions.

Course of Contract: A pilot study preceded the present controlled study of 47 patients. Twenty-five of these were in phase one where maximum valproic acid dose was 30 mg/kg, and 22 in phase two where the maximum was 60 mg/kg.

Major Findings: Long-term EEG telemetry and video recording were used as the primary measure of efficacy for evaluating treatment differences during this clinical trial. During period one of the study, seizures were completely controlled in six (85.7%) of the 7 naive patients who received VPA (valproic acid), and in 4 (44.4%) of 9 naive patients treated with ethosuximide. Although this difference is not statistically significant, p greater than 0.05, it does suggest that VPA is more efficacious than ethosuximide in reducing generalized spike-wave bursts on telemetered EEG. When analyzing results from both period one and two of the study, 37.5% of the naive patients had a 100% reduction in seizure frequency on VPA, but not on ethosuximide, and 12.5% on ethosuximide but not on VPA. Because 37.5% of the naive patients responded to either VPA or ethosuximide, the overall response was 75% to VPA and 50% to ethosuximide. This difference is not statistically significant, but suggests that for naive patients VPA is more efficacious than ethosuximide in reducing generalized spike-wave bursts on telemetered EEG. In refractory patients, a similar finding was produced although again not statistically significant. No patients dropped out of the study because of side effects--they were generally mild and responded to dosage reduction of VPA.

Proposed Course: Seventy patients previously entered into the absence drug studies have been investigated again. Part of the follow-up studies have been reported.

Publications:

Sato S, Penry JK, White BG, Dreifuss FE, and Sackellares JC. Double-blind crossover study of sodium valproate and ethosuximide in the treatment of absence seizures. Neurology (Minneap) 29: 603, 1979.

Sato S, Dreifuss FE, Penry JK and Kirby DK. Prognostic factors in absence seizures: long-term follow-up study. Neurology (Minneap) 30:392, 1980.

C.T. No. 0700759

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1979--September 30, 1980

SOUTHERN RESEARCH INSTITUTE (N01-NS-0-2327)

Title: Studies of Toxicology and Selected Pharmacology of Potential Anticonvulsant Drugs

Contractor's Project Director: Steadman H. Harrison, Ph.D.

Current Annual Level: $278,524

Objectives:
1) Oral Toxicity of Candidate Anticonvulsant Compounds in Rats: The purpose of this phase of the proposal is to expose toxicologic effect of candidate compounds on a variety of organ systems of the rat. There are two steps to this phase: a dose-range finding study, and a 90-day oral toxicity study. The information obtained in the former will be extremely important to the 90-day study; the results will be transmitted to the NINCDS Project Officer within 21 working days following termination of the first part of this study.
2) Cardiovascular Pharmacology of Candidate Anticonvulsant Compounds: The purpose of this phase of the project will be to study the effects of candidate anticonvulsant drugs on the cardiovascular system of unanesthetized beagles. The method used should be designed to give maximum amounts of information without introducing artifacts into the data.
3) Cardiovascular Response of Candidate Anticonvulsant Drugs in Anesthetized Mongrel Dogs: Mongrel dogs are to be anesthetized, ventilated, and catheterized to measure the following parameters: (a) mean arterial blood pressure; (b) mean venous blood pressure; (c) mean pulmonary arterial pressure; (d) heart rate; (e) cardiac output; (f) maximum left ventricular change in pressure per unit of time; (g) systemic resistance; and (h) pulmonary vascular resistance.

Course of Contract: Compounds which have completed the early pharmacologic evaluation of anticonvulsant drug screening contract have been reviewed by the Subcommittee on Anticonvulsant Drugs and been given priority for toxicological evaluation. Supplies of these compounds are now being requested for this contract. This contract has a 3-year period and will end February 1983.

Proposed Course of Contract: The contract began March 1, 1980. The acquisition of beagles and rats for a 90-day study was then made. The dogs are quarantined for baseline hematologic and physiologic evaluation, as drugs are prepared by the supplier in sufficient quantities for the 90-day toxicologic studies. Dosage formulation and stability are also carried out. One drug has been supplied in sufficient quantities to carry out a dose-range finding study and a 90-day study in beagle dogs. Two additional compounds are being prepared by a second supplier for two 90-day rat studies. Nine compounds that have completed the early pharmacologic evaluation of anticonvulsant drugs are then given priority by the Epilepsy Branch for evaluation of toxicology and selected cardiovascular pharmacology. As of July 1, 1980, 3 compounds have been chosen, one for toxicology in beagle dogs and two for toxicology in rats. One rat and one dog toxicological evaluation is required for the Investigational New Drug (IND) application before human testing can begin. The supplier of these compounds has agreed to carry out one study and NINCDS the other.

Publications: None

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1979--September 30, 1980

UNIVERSITY OF WASHINGTON (N01-NS-1-2282)

Title: Study of Experimental Anticonvulsant Drugs in Animals

Contractor's Project Director: Joan S. Lockard, Ph.D.

Current Annual Level: $494,000

Objectives: To compare the anticonvulsant efficacy of drugs in primates with spontaneous motor seizures. Seizure frequency and behavioral toxicity are compared with drug dosage and drug blood concentration. Metabolic and pharmacokinetic studies are conducted.

Course of Contract: Since this anticonvulsant drug research contract in the primate was awarded competitively in June 1971, it has been highly effective and productive. The first 18 months were devoted to the validation of the primate model of focal seizures. A series of quantitative drug evaluations were then performed. These studies were efficacy of anticonvulsants, documentation of the role of social factors in drug therapy, single dose pharmacokinetic experiments, long-term studies, and mass-spectrometry of metabolites of anticonvulsant drugs.

Major Findings: During the year studies were undertaken to determine the effect of clonazepam in this seizure model. It was found that plasma concentrations of 30 and 60 μg/ml were efficacious in the primate focal motor and secondarily generalized tonic-clonic seizures. Seizure frequency, duration, severity, and number of EEG interictal spikes decreased in the majority of monkeys during chronic administration of clonazepam. Some drug tolerance and withdrawal effects were noted. Further, during clonazepam withdrawal there was an increase in seizure frequency even when the plasma concentration was within the therapeutic range. This suggests a possible drug management problem. There was also an unexplained decrease in clearance of clonazepam as a function of chronic administration. This may provide unanticipated higher plasma concentrations after some duration of treatment. Endogenous oscillation in plasma concentrations were found with clonazepam; circadian changes in clearance may be implicated in this phenomenon. The primate data suggests clonazepam as a "broad spectrum" anticonvulsant.

An investigational anticonvulsant--cinromide--was evaluated in four studies. The parent drug has a biological half-life in the monkey of 1 to 2 hours and its active metabolite, 3-bromo-cinnamamide, has a half-life of 4 to 6 hours. Two studies suggest that cinromide is efficacious at a plasma concentration range of 7 to 14 μg/ml of the metabolite; one of six animals showed secondarily generalized seizures during drug administration. The other five animals showed no such seizures. The minimal side effects were observed at these plasma concentrations and some withdrawal seizures seen with cessation of the drug. The metabolite was effective in half of the animals in another study suggesting that the drug's efficacy is individual specific. Some monkeys were not effectively treated regardless of plasma concentration of the metabolite. These studies suggest that controlled studies in man should monitor plasma concentrations of the parent drug and the metabolites in connection with their evaluation for efficacy.

Proposed Course: At present studies are under way to compare the efficacy in status epilepticus of carbamazepine, phenytoin, phenobarbital, diazepam, and valproic acid. Also, the kinetic properties of progabide, a European investigational antiepileptic drug, will be completed. Pursuant to the Institute's policy of competitive procurement, this contract will end August 30, 1980. A Request for Proposals has been released and it is anticipated that a new contract will be awarded September 1, 1980.

Publications:

Patel IH, and Levy RH. Intramuscular absorption of carbamazepine in rhesus monkeys. Epilepsia 21: 103-109, 1980.

Lockard JS, Levy RH, DuCharme LL, and Congdon WC. Cinromide's metabolite in monkey model: gastric administration and seizure control. Epilepsia 21:177-182, 1980.

Lockard JS, and Wyler AR. The influence of attending on seizure activity in epileptic monkeys. Epilepsia 20:157-168, 1979.

Lai AA, and Levy RH. Pharmacokinetic description of drug interactions by enzyme induction: carbamazepine-clonazepam in monkeys. J Pharm Sci 68:416-421, 1979.

Lai AA, Min BH, Garland WA, and Levy RH. Kinetics of biotransformation of clonazepam to its 7-amino metabolite in the monkey. J Pharmacokinet Biopharm 7:87-95, 1979.

Lockard JS, Levy RH, DuCharme LL, Congdon WC, and Patel IH. Carbamazepine revisited in a monkey model. Epilepsia 20:169-173, 1979.

Harris AB, and Lockard JS. Macaca fascicularis: alternative epileptic model. Life Sci 16:281-286, 1979.

Lockard JS, Levy RH, DuCharme LL, and Congdon WC. Experimental anticonvulsant cinromide in monkey model: preliminary efficacy. Epilepsia 20:339-350, 1979.

Lockard JS, Levy RH, Congdon WC, DuCharme LL, and Salonen LD. Clonazepam in a focal-motor monkey model: efficacy, tolerance, toxicity, withdrawal, and management. Epilepsia 20:683-695, 1979.

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1979--September 30, 1980

UNIVERSITY OF KANSAS MEDICAL CENTER (N01-NS-2-2313)

Title: Investigation of Pharmacologic Posttraumatic Epilepsy Prophylaxis

Contractor's Project Director: Charles Brackett, M.D.

Current Annual Level: $100,000

Objectives: A study to determine the effectiveness of therapeutic treatment with phenytoin and phenobarbital in persons who suffer severe head injury and are thus liable to posttraumatic epilepsy. This study was preceded by a pilot study with prophylactic doses.

Course of Contract: One hundred and twenty-five patients were accessioned in the pilot study, and all have completed the required 18-month treatment, and the remaining eligible patients were also followed for another 18-month period of no drug treatment. Eleven patients experienced seizures while on the study, and four had seizures after completion of drug therapy. Results of this pilot study are currently in preparation for publication. The continuation of the study in severely injured patients with therapeutic doses of phenobarbital and phenytoin stopped admission of patients as of 12/1/79. Of the 49 patients admitted, all eligible patients will complete the 12 months of drug treatment by 7/4/81. Nine patients have experienced seizures as of 2/6/80, 8 placebo and 1 active patient.

Proposed Course of Contract: The overall results of the pilot study are in preparation. Also, there will be additional investigation into the relationship between study drug doses and plasma levels. The current study utilizing therapeutic dosages will continue followup of the remaining 49 patients.

C.T. No. 0700757

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1979--September 30, 1980

EXCERPTA MEDICA FOUNDATION (N01-NS-3-2303)

Title: Publication of *Epilepsy Abstracts*, Volume 13

Contractor's Project Director: Pierre Vinken, M.D.

Current Annual Level: $55,000

Objectives: To scan serial publications and periodicals from approximately 3500 world biomedical journals and select appropriate articles to be included in *Epilepsy Abstracts* in accordance with the guidance of the Project Officer and his editorial advisors; prepare abstracts with appropriate translations into English from foreign languages; classify, index, and store the abstracts in a computer retrievable form; and produce a 9-tract, 1600 bpi computer tape for use at NIH. The text is automatically set by computer-operated photocomposition. The Excerpta Medica Foundation produces camera-ready copy for each monthly issue of *Epilepsy Abstracts*, which includes an index of subjects and authors, and prints and distributes the journal monthly with a cumulative index at the end of the volume. In order to pay for the production of the camera-ready copy, printing, and distribution, the Excerpta Medica Foundation sells subscriptions to recover these costs.

Course of Contract: Subscriptions to *Epilepsy Abstracts*, each at annual cost of $77.00, have been acquired from interested persons by Excerpta Medica at a satisfactory rate. Interest in the publication continues at a high level throughout the world.

Proposed Course of Contract: Continued publication of monthly issues of *Epilepsy Abstracts*; computer tapes delivered to NIH bimonthly in accordance with the contract. These tapes comprise the EPILEPSYLINE data base retrievable throughout the country from the National Library of Medicine.

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1979--September 30, 1980

STANFORD RESEARCH INSTITUTE (N01-NS-3-2322)

Title: Continued Development of a Wearable Eight-Channel EEG Cassette Recording System

Contractor's Project Director: Charles S. Weaver, Ph.D.

Current Annual Level: -0-

Objectives: The objectives of this project are to fabricate, maintain and evaluate a wearable EEG recording system; to design and fabricate an economical playback system without computer tape format; and to design a data compression scheme. This development includes a hybridized amplifier system to provide for eight channels of differential recording connected to a wearable tape recorder with appropriate signal processing electronics. Digital encoding circuitry provides for a full dynamic range and suitable bandwidth to allow for automatic processing of EEG data by computer. In addition to the design and development of the recording technique and implementation in hardware, the overall system is to be clinically evaluated with a selected group of patients under environmental conditions similar to those in which it will ultimately be used. The playback system is to transcribe the encoded data from initial tape cassettes and reform the original analog EEG on a strip chart through micro-processor, as well as to interface to a computer.

Major Findings: The first eight-channel recorder and playback system was delivered on December 3, 1976. Now, two on-body systems with hybridized amplifiers are in use. The system weighs approximately five pounds and records eight leads of EEG for twelve hours on a standard C-120 audio cassette with a bandwidth of 40Hz. The system successfully underwent engineering evaluation and was accepted in March 1977. It is now undergoing extensive clinical evaluation at the Clinical Center, NIH, and elsewhere. Reliability and reproducibility have been tremendously improved by wiring in the headpiece and modification of digital circuits in the playback system. On June 13, 1980 the low-cost playback system was delivered and since then has been subjected to field evaluation. Delivery of further hybridization of the on-body system took place late in the fiscal year. This on-body system weighs 50% less, is 40% reduced in size, and uses 50% less power than the previous recorder. Planning is well underway for transfer of this new technology to allow commercial production of the recording system.

Significance to NINCDS Program and Biomedical Research: The availability of a lightweight high-fidelity portable EEG tape recorder will allow significant improvement in both diagnosis and therapy of some types of epilepsy, and provide numerous research opportunities, e.g., evaluation of drug treatment of seizures.

Proposed Course of Contract: The contract expired in September 1979.

Collaborating Units: This project was carried out as a collaborative effort of the Neurological Disorders Program and the Fundamental Neurosciences Program. The Neurological Disorders Program has provided the clinical direction and the funding, while the Fundamental Neurosciences Program provided the technical direction and project management.

Publications: None

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1979--September 30, 1980

UNIVERSITY OF UTAH (N01-NS-5-2302)

Title: Early Pharmacologic Evaluation of Anticonvulsant Drugs

Contractor's Project Director: Ewart A. Swinyard, Ph.D.

Current Annual Level: $335,000

Objective: To determine the anticonvulsant properties of novel organic compounds at various levels of testing from preliminary screening to extensive activity and toxicity profiles.

Course of Contract: Compounds are received by NINCDS from academic and industrial medicinal chemists and sent to the University of Utah for testing. Initially, the levels of anticonvulsant and neurotoxicity activities are determined on all compounds submitted. For those compounds which exhibit anticonvulsant activity without signs of neurological deficit, the ED_{50} and TD_{50} are determined. The pharmacologic data is then provided to NINCDS where it is reviewed and analyzed. The submitters of compounds are then informed of the results and any proposed additional testing, which may be warranted. Those compounds which are selected as the most promising are scheduled for advanced testing (Phases III-VII). The advanced phases of testing incorporate the oral route of administration (all preceding testing performed intraperitoneally) using the mouse and rat along with a complete toxicity profile and drug characterization of doses at 1, 2, and 4 times the TD_{50} of the compound given intraperitoneally in mice. Recently included in the advanced phases of testing is an antiepileptic drug differentiation testing whereby 4 chemically induced seizure models are used to predict possible modes of action as compared to the currently marketed antiepileptic drugs. Another recent addition to the advanced testing is an oral LD_{50} determination in rat.

Proposed Course of Contract: This program began January 1, 1975 and during the period October 1, 1979 through September 30, 1980 screened 1,000 compounds for anticonvulsant activity. Currently, 65 compounds have been scheduled for the advanced phases of testing with 20 compounds completing all of these phases. An RFP for a new contract has been issued with TMR review in August and funding October 1, 1980 for a 3-year period.

Publications: None

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1979--September 30, 1980

Contractor		Project Director	Annual Level
Univ of Minnesota	(N01-NS-5-2327)	R. Gumnit, M.D.	$1,996,281
Good Samaritan Hosp Portland	(N01-NS-5-2328)	J. Schimschock, M.D.	866,000
Univ Va Med Center	(N01-NS-5-2329)	F. Dreifuss, M.D.	1,045,486
Med Coll Georgia	(N01-NS-6-2340)	J. Green, M.D.	1,156,259
Univ of Washington	(N01-NS-6-2341)	A. Ward, Jr., M.D.	1,055,974

Title: Comprehensive Epilepsy Program

Objectives: The objective of the Comprehensive Epilepsy Program is to facilitate applied research and to coordinate research and teaching with health care services related to persons with all types of epileptic seizures within a defined geographic area.

Course of Contract: Each contractor is conducting clinical and laboratory research in the diagnosis, treatment, prognosis and prevention of epilepsy. Each contractor is demonstrating to physicians and other professionals the newest advances in epilepsy research and treatment and is establishing a broad program for public education. In addition, each contractor is establishing the required procedures to assure, in a research setting, the availability to the person with epilepsy of complete and up-to-date preventive medical and rehabilitative psychological, vocational, educational, and social services.

Major Findings: During fiscal year 1975 three Comprehensive Epilepsy Programs were established. During fiscal year 1976 two additional programs were established. All of the contractors showed evidence for the feasibility of establishing a program in their geographic area by a detailed description of clinical research capability, health care delivery, rehabilitation, resources, etc., for the person with epilepsy. All of the programs underwent Technical Merit Review prior to beginning of the fourth year.

Proposed Course of Contract: During the coming year, the Comprehensive Epilepsy Programs will facilitate applied research and coordinate research and teaching with health care services related to persons with all types of epileptic seizures within their defined geographic area. Inpatient facilities will be made available to patients for periods of 3-6 months to receive special diagnostic evaluation and intensive treatment of their seizure disorders and any other concurrent handicap or physical problem. Vocational training, psychological support, other ancillary services and continued schooling will be simultaneously provided. Existing services will be coordinated for maximum utilization. An integral part of the program will be demonstration at all levels in the management of patients with epilepsy for professionals, paraprofessionals, and the lay public. While it is recognized that care for persons with epilepsy is available from many sources at the present time, these are scattered and noninclusive so that a patient may or may not receive total care depending on the local resources and how well they are coordinated. The University of Minnesota has been funded as a P50 grant beginning July 1, 19[illegible]0; the Good Samaritan Hospital and the University of Virginia have applied for grant funding, also.

Publications:

University of Minnesota:

Annegers JF, Grabow JD, Laws Jr ER, Kurland LT: The incidence, causes and secular trends of head trauma in Olmsted County, 1935-1974, *Am J Epidemiol* 110:364, 1979.

Annegers JF, Groover RV: Seizure disorders and congenital malformations in the offspring of parents with epilepsy. *Int J Epidemiol* 7:241-247, 1978.

Annegers JF, Hauser WA, Elveback LR: Remission of seizures and relapse in patients with epilepsy. *Epilepsia* 20:729-737, 1979.

Annegers JF, Kurland LT: The epidemiology of central nervous system trauma. In *Central Nervous System Trauma*, edited by GL Odom, National Institutes of Health, p 108, 1979.

Annegers JF, Kurland LT, Hauser WA: Brain tumors in children exposed to barbiturates. *J Natl Cancer Inst* 63:3-4, 1979.

Annegers JF, Laws Jr ER, Kurland LT, Grabow JD: Head trauma and subsequent brain tumors. *Neurosurg* 4:203-206, 1979.

Bataldin P, VanDyne B, Cloyd JC: Pancreatitis associated with valproic acid - a case report. *Pediatrics* 64:520-522, 1979.

Beniak J, Miller D, Blesi K: The reality of epilepsy: an up-to-date approach for patients and practitioners. *J Prac Nurs* 30:22-26, 1980.

Brings DM: Epilepsy-specific educational needs of medical and allied health professionals: An intervention and utilization-focused assessment. In *Advances in Epileptology: The Xth Epilepsy International Symposium*, edited by J Wada and JK Penry, Raven Press, New York, 1980.

Cloyd JC, Bosch DE, Sawchuk RJ: Concentration-time profile of phenytoin after admixture with small volumes of intravenous fluids. *Am J Hosp Pharm* 35:45-48, 1978.

Cloyd JC, Lesar T, Gumnit RJ: Reduced seizure control due to spoiled phenytoin capsules. *Ann Neurol* 7:191-193, 1980.

Coulam CB, Annegers JF: Do anticonvulsants reduce the efficacy of oral contraceptives for contraception? *Epilepsia* 20:519-526, 1979.

Grabow JD, Aronson AE, Greene KL, Offord KP: A comparison of EEG activity in the left and right cerebral hemispheres by power spectrum analysis during language and non-language tasks. *Electroencephalogr Clin Neurophysiol* 47:460-472, 1979.

Grabow JD, Aronson AE, Offord KP, Rose DE, Greene KL: Hemispheric potentials evoked by speech sounds during discrimination tasks. *Electroencephalogr Clin Neurophsyiol* 49:48-58, 1980.

Grabow JD, Aronson AE, Rose DE, Greene KL: Summated potentials evoked by speech sounds for determining cerebral dominance for language. *Electroencephalogr Clin Neurophysiol* 49:38-47, 1980.

Hauser WA: Epidemiology of epilepsy. In *Advances in Neurology*, Vol. 19, edited by BS Schoenberg, Raven Press, New York, pp 313-339, 1978.

Jacome DE, Gumnit RJ: Audioalgesic and audiovisualgesia synesthesias: epileptic manifestations. *Neurology* (Minneap) 29:1050-1053, 1979.

Jacome DE, McLain LW, Fitzgerald R: Postural reflex gelastic seizures. *Arch Neurol* 37:249, 1980.

Leppik IE, Cloyd JC, Sawchuk RJ, Pepin SM: Compliance and variability of plasma phenytoin levels in epileptic patients. *Ther Drug Monitor* 1:475-483, 1980.

Lockman LA, Kriel K, Thompson T, Virnig N, Zaske D: Phenobarbital dosage for control of neonatal seizures. *Neurology* (Minneap) 29:1445-1449, 1979.

Parvin C, Torres F, Johnson EA: Synchronization of single evoked response components: estimation and interpretation of reproducibility measures. In *Rhythmic EEG Activities and Cortical Functioning*, edited by D. Pfurtscheller, et al., Elsevier, Holland, pp 203-217, 1980.

Ramani SV, Quesney LF, Olson D, Gumnit RJ: Diagnosis of hysterical seizures in epileptic patients. *Am J Psychiatr* 137:705-709, 1980.

Sawchuk RJ, Cartier LL: Liquid-chromatographic method for simultaneous determination of phenytoin and 5-4-hydroxyphenyl-5-phenylhydantoin in plasma and urine. *Clin Chem* 26:835-839, 1980.

Sawchuk RJ, Rector TA, Fordice JJ, Leppik IE: Effects of influenza vaccination on plasma phenytoin concentrations. *Ther Drug Monitor* 1:285-288, 1979.

Sawchuk RJ, Rector TS: Steady-state plasma concentrations as a function of the absorption rate and dosing interval for drugs exhibiting concentration-dependent clearance: consequences for phenytoin therapy. *J Pharmacokinet Biopharm* 7:543-555, 1979.

Walton SAV: Epilepsy follow-up: dispensing facts, dispelling fears. *J Prac Nurs* 30:25-26, 39, 1980.

Walton SAV: Teaching children about epilepsy. *Educ Unlim* 1:16-19, 1979.

Whisler JW, Johnston D: Epileptogenesis: a model for the involvement of slow membrane events and extracellular potassium. *J Theoret Biol* 75:271-288, 1978.

Yanagihara T: Protein and RNA syntheses and precursor uptake with isolated nerve and glial cells. *J Neurochem* 32:169, 1979.

Good Samaritan Hospital and Medical Center:

Ash PR, Smith WB: Micro myoclonic seizures of sleep. *Arch Neurol* 36:575-577, 1979.

Gabourel JD, Bardana EJ, Davies GH, Smith RL: IgA depression and changes in cellular immunity during phenytoin therapy. *Pharmacologist* 21:245, 1979.

Gerber N, Thompson RM, Smith RG, Lynn RK: Significance of the epoxide-diol pathway in the biotransformation of mephenytoin. *Epilepsia* 20:287-294, 1979.

Gerber N, Dickinson R, Harland R, Lynn RK, Houghton D, Antonias J, Schimschock JR: Reye-like syndrome associated with valproic acid therapy. *J Pediatr* 95:142, 1979.

Laxer KD, Robertson LT, Julien RM, Dow RS: The relationship between cerebellar function and epileptic discharges. In *Antiepileptic Drugs: Mechanisms of Action*, edited by GH Glaser, JK Penry, DM Woodbury, Raven Press, New York, pp 415-418, 1980.

Riker WK, Downes H, Olsen GD, Smith BW: Conjugate lateral gaze nystagmus and free phenytoin concentrations in plasma: lack of correlation. *Epilepsia* 19:93-98, 1978.

Robertson LT, Dow RS, Cooper IS, Levy LF: Morphological changes associated with chronic cerebellar stimulation in the human. *J Neurosurg* 51:510-520, 1979.

Skinner SF, Robertson LT, Artero M, Gerding RK: A longitudinal study of phenobarbital in serum, CSF, and saliva in the dog. *Am J Vet Res* 41:600-605, 1980.

University of Virginia:

Boll TJ: Diagnosing brain impairment. In *Diagnosis of Mental Disorders: A Handbook*, edited by B Wolman, Plenum Press, New York, pp 601-674, 1978.

Boll TJ, Dimino E, Mattson AW: Parenting attitudes: The role of personality style and childhood long-term illness. *J Psychosom Res* 22:209-213, 1978.

Boll TJ, Richards H, Berent S: Tactile perceptual functioning and academic performance in brain impaired and unimpaired children. *Percept Mot Skills* 47:491-495, 1978.

Dreifuss FE: The use of anticonvulsant drugs. JAMA 241:607-609, 1978.

Dreifuss FE: The development of a comprehensive epilepsy program. In Modern Perspectives in Epilepsy, edited by J Wada, Eden Press, Montreal, 1978.

Dreifuss FE: Partial seizures. In Textbook of Pediatric Neurology, edited by Swaiman and Wright, Mosby Co., St. Louis, 1980.

Dreifuss FE: Post-traumatic epilepsy. In Lawyers Medical Cyclopedia, Suppl. 32:47-58, edited by C Frankel, Allen Smith Co., Indianapolis, 1980.

Dreifuss FE: Perspectives on the management of epilepsy. In Phenytoin-Induced Teratology and Gingival Pathology, edited by TM Hassell, MC Johnson, KH Dudley, Raven Press, New York, 1980.

Ellis JM, Lee SI: Acute prolonged confusion in later life as an ictal state. Epilepsia 19:119-128, 1978.

Fowler P: Factor structure of the preschool behavior questionnaire in a normal population. Psychol Rep 45:599-606, 1979.

Sackellares JC, Dreifuss FE: The treatment of epilepsy in children. Curr Prescribing 5:63-77, 1979.

Sackellares JC, Lee SI, Dreifuss FE: Stupor following administration of valproic acid to patients receiving other antiepileptic drugs. Epilepsia 20:697-703, 1979.

Santilli N, Dreifuss FE: Pediatric management problems (absence seizures). Pediatr Nurs July/Aug, 1979.

Redenbaugh JE, Sato S, Penry JK, Dreifuss FE, Kupferberg HJ: Sodium valproate: pharmacokinetics and effectiveness in treatment of intractable seizures. Neurology 30:1-6, 1980.

Medical College of Georgia:

Mercille RA, Green JB, Katter G, Deaver H: The training of community epilepsy teams by the Georgia Comprehensive Epilepsy Program. In Epileptology -- The Xth Epilepsy International Symposium, edited by JA Wada, JK Penry, Raven Press, New York, 1980, pp 389-393.

Smith DB: Antifolate-antiepileptic relationships. In Folic Acid in Neurology, Psychiatry and Internal Medicine, edited by IM Botez, EM Reynolds, Raven Press, New York, 1979, pp 267-283.

University of Washington:

Dodrill CB, Batzel LW, Queisser HR, Temkin NR: An objective method for the assessment of psychological and social problems among epileptics. Epilepsia 21:123-135, 1980.

Fraser RT: Approaching employers for job development and job analysis. In *Training Manual in Job Placement*, edited by A Livingston, T Korn, 1979, pp 51-59.

Friel PN, Leal KW, Wilensky AJ: Valproic acid-phenytoin interaction. *Ther Drug Monitor* 1:243-248, 1979.

Leal KW, Rapport RL, Wilensky AJ, Friel PN: Pharmacokinetics of primidone in mice after acute and chronic administration. *Drug Metab Distri* 7:345, 1979.

Levy RH, Cenraud B, Loiseau P, Akbaraly R, Brachet-Liermain A, Guyot M, Gomeni R, Morselli PL: Meal-dependent absorption of enteric-coated sodium valproate. *Epilepsia* 21:273-280, 1980.

Oakley JC, Ojemann GA, Ojemann LM, Cromwell L: Identifying epileptic foci on contrast enhanced CT scans. *Arch Neurol* 36:669-671, 1979.

Patel IH, Levy RH, Cutler RE: Phenobarbital-valproic acid interaction. *Clin Pharm Ther* 27:515-521, 1980.

Troupin AS, Friel PN, Lovely MP, Wilensky AJ: Clinical pharmacology of mephenytoin and ethotoin. *Ann Neurol* 6:410-414, 1979.

Troupin AS, Wilensky AJ, Friel PN, Leal KW, Ojemann LM: Clorazepate as an anticonvulsant. *Antiepileptic Therapy*: *Advances in Drug Monitoring*, edited by SI Johannessen, PL Morselli, CE Pippenger, A Richens, D Schmidt, H Meinardi, Raven Press, New York, 1980, pp 291-298.

Wilson JM, Friel PN, Wilensky AJ, Raisys VA: A methods comparison: clonazepam by gas chromatography-electron capture and gas chromatography-mass spectroscopy. *Ther Drug Monitor* 1:387-397, 1980.

CONTRACT NARRATIVE
Neurological Disorders Program--Epilepsy Branch
October 1, 1979--September 30, 1980

THE METHODIST HOSPITAL (Houston, Texas) (NO1-NS-9-2321)

Title: Treatment of Infantile Spasms

Contractor's Project Director: Peter Kellaway, M.D.

Current Annual Level: $130,000

Objectives: To conduct a controlled evaluation of corticotropin and prednisone in 25 patients with infantile spasms. Children who do not respond to either treatment will be administered clonazepam in an open trial. Precise quantitation methods were developed in a predecessor contract.

Course of Contract: Since award of the contract, 5 patients have been admitted. Because the study is blinded, results will not be available until its completion.

Major Findings: The comparative results of the three drug treatments of infantile spasms will not be known until the study is completed in late 1981.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 NS 01933 10 EB

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Quantitation of Spike-Wave Activity by a Reaction Time Method

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.:	Susumu Sato	Neurologist	EB NDP NINCDS

COOPERATING UNITS (if any) F.E. Dreifuss, M.D., Prof. of Neurol., Dept. of Neurol., Univ. of Virginia, Charlottesville, VA; J.K. Penry, M.D., Prof. of Neurol., Bowman Gray School of Med., Winston-Salem, NC

LAB/BRANCH
Epilepsy Branch, NDP, NINCDS

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 0.2	PROFESSIONAL: 0.1	OTHER: 0.1

CHECK APPROPRIATE BOX(ES)

X (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study determines whether reaction time in absence patients is or is not impaired in a gradual fashion from the point of spike-wave initiation. A reaction-time device is employed which gives instantaneous recognition by voltage criteria that a spike-wave burst has started. This burst is of much higher than normal background, and this factor alone is used to electronically trigger the reaction timer. On instantaneous recognition the reaction time is triggered and a tone is delivered to the subject. The subject responds by turning off the high pitch tone with a telegraph key. Between paroxysms the patient is maintained in a state of alertness.

PHS-6040
(Rev. 10-76)

Project Description:

Objectives: To determine whether reaction time in patients with absence (petit mal) seizures is or is not impaired in a gradual fashion from the point of spike-wave initiation as has been suggested by some authorities but disputed by others. There is some evidence for a "trough-like" pattern decrease of consciousness. The onset of decreased clinical functions during spike-wave paroxysms is evaluated by the reaction time method.

Methodology: A device is employed which gives instantaneous recognition by voltage criteria that a spike-wave burst has started. This burst is of much higher than normal background, and this factor alone is used to electronically trigger the reaction time. On instantaneous recognition the reaction timer is triggered and a tone is delivered to the subject. The subject responds by turning off the high pitch tone with a telegraph key. Between paroxysms the patient is maintained in a state of alertness by a program of approximately 10 random stimuli per minute. All the data is collected by television, including a portion of the screen reserved for the reaction time from the digital clock. There is no age limit in selecting patients, but they must all have spike-wave paroxysmal discharge. A second group of patients was studied with the apparatus altered slightly so that the auditory stimulus was delivered 0.5 seconds into the seizure in order to see if responsiveness becomes less as the seizure progresses. Oscillographic displays from magnetic tape recordings of spike-wave paroxysms revealed shifting asymmetries.

Major Findings: The first group of patients suggests that some ability to respond early during the paroxysmal burst is maintained; this responsiveness is frequently not seen 1-2 seconds after onset. Analysis of responsiveness during short bursts suggests that patients may retain a normal reaction time during such paroxysms.

Significance to NINCDS Program and Biomedical Research: This study has applied video recording techniques and sophisticated electronic methods to improve the quality of clinical research. Specifically, this study is an analysis of the relation of the patient's behavior to his EEG during paroxysmal electroencephalographic events. An understanding of this relationship is important--not only as a guidepost for further research in the mechanism of epilepsy, but also in determining the day-to-day therapeutics of the epileptic patient.

Proposed Course of Contract: With the completion of patients evaluated in a follow-up study of earlier accessions into drug evaluation protocols, this project has been completed.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02097 09 EB

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Diagnostic Value of Prolonged Telemetered EEG in Epilepsy

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.:	Susumu Sato	Neurologist	EB NDP NINCDS

COOPERATING UNITS (if any) W.L. Brannon, M.D., Chief, Neurology Service, U.S. Naval Med. Cen., Charleston, SC; J.K. Penry, M.D., Prof. of Neurology, Bowman Gray School of Med., Winston-Salem, NC

LAB/BRANCH
Epilepsy Branch, NDP, NINCDS

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.1	0.1

CHECK APPROPRIATE BOX(ES)

X (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Telemetered EEGs are recorded for 6 hours in order to sample over a longer period of time than the usual 20-30 minutes, and during normal activity. The incidence of diagnostic paroxysmal abnormalities in the 6-hour telemetered EEG are compared with those from routine conventional EEGs. About 10% of patients have had diagnostic abnormalities on the 6-hour telemetered EEG which were not recorded in the routine EEG. The ability to detect and record diagnostic epileptiform abnormalities in the EEG after a single seizure will aid in the early treatment and long-term prognosis of patients who suffer their initial seizure.

Project Description:

Objectives: To develop a means of detecting and recording interictal paroxysmal abnormalities (epileptiform) in the EEG of patients who have suffered a clinical convulsion.

Methodology: Telemetered EEGs are recorded for 6 hours in order to sample over a period of time longer than the usual 20-30 minutes and during normal activity; in some patients, the latter may evoke interictal paroxysmal abnormalities in the 6-hour telemetered EEG when compared with those from routine conventional EEGs. One hundred patients have been evaluated.

Major Findings: In the initial group of patients studied, about 10% have had diagnostic abnormalities on the 6-hour telemetered EEG which were not recorded in the routine EEG. The accessioning of patients has been completed and the results will be analyzed and published in the near future.

Significance to NINCDS Program and Biomedical Research: If patients could be identified before the occurrence of a seizure, they could be treated and the seizure prevented--without treating those patients who will not have a recurrence.

Proposed Course of Project: This project has been concluded.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01-NS-02437 01 EB

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Stable Isotope Methodology in a Pharmacokinetic Study of Phenobarbital

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.:	Izet M. Kapetanovic	Pharmacologist	EB NDP NINCDS
Other:	Harvey J. Kupferberg	Pharmacologist	EB NDP NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Epilepsy Branch, NDP, NINCDS

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 0.3	PROFESSIONAL: 0.3	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A pharmacokinetic study of stable isotopically labeled phenobarbital in epileptic patients was carried out. Plasma concentration-time profiles of the stable isotopically labeled phenobarbital were monitored by GCMS computer system. The pharmacokinetics of phenobarbital were determined at a time when the patient was in steady-state in terms of unlabeled phenobarbital. Labeled phenobarbital could be quantitated to 0.3 μg/ml when the labeled phenobarbital plasma levels were 90 μg/ml. The pharmacokinetic parameters were: $k_{el} = 0.0055$ hr^{-1}, $t_{1/2} = 126$ hr, $V_D = 34.3$ liters and total clearance = 189 ml/hr^{-1}. These data will be used as control values and compared to those obtained when phenobarbital is given with valproic acid in an effort to determine the mechanisms for this drug-drug interaction.

PHS-6040
(Rev. 10-78)

Project Description:

Objectives: To establish the usefulness of stable isotope methodology, gas chromatography-mass spectrometry as a tool for determining pharmacokinetic parameters of absorption, elimination and clearance of antiepileptic drugs.

Major Findings: The use of stable isotope methodology combined with gas chromatography-mass spectrometry may be used in determining absorption, distribution and elimination kinetics, volumes of distribution and clearance of antiepileptic drugs in a variety of clinical projects, e.g., drug-drug interactions.

Significance to NINCDS Program and Biomedical Research: Pharmacokinetic parameters of antiepileptic drugs are essential in many clinical studies. These parameters are usually determined by either withdrawing the drug or by single dose administration. These techniques are not viable alternatives in patients on chronic therapy.

Proposed Course: This project has been completed.

Publications:

Kapetanovic IM, Kupferberg HJ: Stable isotope methodology and gas chromatography mass spectrometry in a pharmacokinetic study of phenobarbital. Biomed Mass Spectrom 7:47-52, 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-NS-02438 01 EB

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)
Brain Plasma Levels in Mice of Various 1,5-Cyclopolymethylenetetrazoles (1,5-CPMTZ) at Convulsant Dosages

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.:	Wayne Yonekawa	Pharmacologist	EB NDP NINCDS
Other:	Harvey J. Kupferberg	Pharmacologist	EB NDP NINCDS

COOPERATING UNITS (if any)
Dixon M. Woodbury, Ph.D., Department of Pharmacology, University of Utah College of Medicine, Salt Lake City, Utah

LAB/BRANCH
Epilepsy Branch, NDP, NINCDS

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 0.3	PROFESSIONAL: 0.3	OTHER:

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The 1,5-CPMTZ homologs of pentylenetetrazole (PTZ) have received only cursory attention, partly because the hydrophobic nature of some makes their administration difficult. We wanted to know if differences in seizure potency of the 1,5-CPMTZs were related to their activity or to their brain uptake. Following i.p. doses (CD_{50} for clonus) in mice, with sesame oil as a vehicle, the brain and plasma level time course of each 1,5-CPMTZ was determined by GLC with N-P detection. The CD_{50}s were: tetramethylenetetrazole (C_4MT), 340 mg/kg (2.74 mmol/kg); PTZ, 63 mg/kg (0.46 mmol/kg); heptamethylenetetrazole (C_7MT), 37 mg/kg (0.22 mmol/kg); octamethylenetetrazole (C_8MT), 140 mg/kg (0.78 mmol/kg); undecamethylenetetrazole ($C_{11}MT$), 150 mg/kg (0.67 mmol/kg). The peak brain level may be a better indicator of convulsant activity than the CD_{50} because of differences in absorption. The peak brain levels were: C_4MT, 3.0 μmol/g; PTZ, 0.33 μmol/g; C_7MT, 0.13 μmol/g; C_8MT, 0.43 μmol/g; $C_{11}MT$, 0.16 μmol/g. We conclude that differences in convulsant activity of the 1,5-CPMTZ homologs result from differences in intrinsic activity and are not a disposition phenomenon.

Project Description:

Objectives: To relate brain levels of a homologous series of cyclopolymethylenetetrazoles to their convulsant activity in mice.

Major Findings: In a series of cyclopolymethylenetetrazoles, maximum convulsant activity was achieved with the heptamethylene homolog. The activity, as measured in mmol/kg, decreased with the higher molecular weight homologs. The brain levels at the CD_{50} were similar in mice receiving the heptyl and undecyl homologs.

Significance to NINCDS Program and Biomedical Research: The convulsant activity in a series of cyclopolymethylenetetrazoles is a function of their intrinsic activity and not a dispositional phenomenon. The most active of this series will be evaluated as a model in experimental epilepsy.

Proposed Course: This project has been completed.

Publications:

Yonekawa WD, Kupferberg HJ, Woodbury DM: Brain plasma levels in mice of various 1,5-cyclopolymethylenetetrazoles (1,5-CPMTZ) at convulsant dosages. Pharmacologist 357, 1980 (abstract).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01-NS-02439 01 EB

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Inhibition of Microsomal Phenobarbital Metabolism by Valproic Acid

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.:	Izet M. Kapetanovic	Pharmacologist	EB NDP NINCDS
Others:	Harvey J. Kupferberg	Pharmacologist	EB NDP NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Epilepsy Branch, NDP, NINCDS

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS: 0.3	PROFESSIONAL: 0.3	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Valproic acid (VPA) has been reported to cause elevation of plasma phenobarbital (PB) levels in epileptic patients. We have found that VPA inhibits the metabolism of PB in epileptic patients and therefore may be responsible for this drug-drug interaction (Pharmacologist 21:208, 1979). We have further studied this interaction in an in vitro system, using hepatic microsomes from adult male PB-treated Holtzman rats. An assay system for microsomal parahydroxylation of PB was developed. Microsomes were incubated at 37°C in the presence of 0.1 M potassium phosphate buffer (pH 7.50) and 0.25 mM NADPH. The microsomal reaction mixture was washed twice with benzene to remove substrate PB, and the p-hydroxyphenobarbital (p-OHPB) was then extracted with ethylacetate. The extract was perethylated with ethyl iodide in acetonitrile in the presence of tetraethylammonium hydroxide. The p-OHPB was quantitated by gas chromatography, using a nitrogen selective flame ionization detector, with diphenylbarbituric acid as the internal standard. VPA was shown to be a competitive inhibitor of microsomal parahydroxylation of PB. The Michaelis constant (Km) was 1.16 mM; maximal velocity (Vmax), 0.325 nmole p-OHPB formed min-1 nmole P450-1; and inhibition constant (Ki), 1.20 mM.

Project Description:

Objective: To determine the biochemical mechanism of valproic acid's inhibition of phenobarbital metabolism.

Major Findings: Valproic acid is a competitive inhibitor of rat liver microsomal parahydroxylation of phenobarbital. The Michaelis constant (Km) is 1.16 mM; maximal velocity (Vmax), 0.325 n/mole parahydroxyphenobarbital formed per minute, per nmole p450; and inhibition constant (Ki), 1.20 mM.

Significance to NINCDS Program and Biomedical Research: This in vitro experiment provides an understanding of valproic acid-phenobarbital interaction in epileptic patients.

Proposed Course: This project is completed.

Publication:

Kapetanovic IM, Kupferberg HJ: Inhibition of microsomal phenobarbital metabolism by valproic acid. Fed Proc 39:1099, 1980 (abstract).

ANNUAL REPORT

October 1, 1979 through September 30, 1980

Developmental Neurology Branch, NDP
National Institute of Neurological and Communicative Disorders and Stroke

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A COMPREHENSIVE PLAN FOR ANALYSIS AND INTERPRETATION OF COLLABORATIVE PERINATAL PROJECT DATA

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ANNUAL REPORT
For Period October 1, 1979 through September 30, 1980
Developmental Neurology Branch, Neurological Disorders Program
National Institute of Neurological and Communicative
Disorders and Stroke
National Institutes of Health

GENERAL SUMMARY

I. INTRODUCTION:

The Developmental Neurology Branch (DNB) develops and implements a program of research on the neurobiological aspects of the developmental disorders of children including cerebral palsy and other motor disorders, autism and behavioral disorders, mental retardation and learning disorders, and central nervous system birth defects and genetic disorders. The DNB is formally organized into sections which correspond to these four subprogram areas. During this year the DNB will be gaining responsibility for grant management of the Disorders of Early Life, a major disorder category within the Neurological Disorders Program.

New initiatives which have received concept clearance and are being developed by the DNB are on Reye's Syndrome, neonatal brain disorders, and a pilot study on the development of an examination battery designed to measure the effect of phenobarbital or other anti-convulsant therapy on the cognitive and neurological status of the treated child.

A program announcement on Reye's Syndrome was published on May 16, 1980 which requested individual and program project research grant applications. This program announcement was co-sponsored by three other NIH institutes. The DNB is serving as the focal point within NINCDS in the planning of a Consensus Development Conference on the Diagnosis and Treatment of Reye's Syndrome for early spring, 1981. The NINCDS is the lead agency for this Consensus Conference in co-sponsorship with the Office for Medical Applications of Research, NIH, the Center for Disease Control, the National Center for Health Statistics and the following NIH institutes: NIAID, NICHD, NIAMD, NIGMS, and NIEHS. The Consensus Conference will focus on the criteria for diagnosis and on the treatments in use, with particular attention to the treatment of the syndrome as a function of the severity of the syndrome.

The initiative on neonatal brain disorders will focus on the pathogenesis, diagnosis, treatment, and outcome of intraventricular hemorrhage in low birthweight neonates, hypoxic-ischemic encephalopathy in full-term infants, neonatal seizures, and metabolic disorders relevant to neonatal brain function.

The effect of anticonvulsant medication, particularly phenobarbital, on the developing nervous system has been a major concern of the DNB. The Consensus Conference on Febrile Seizures also emphasized this concern, and a program initiative is underway to develop an examination battery which will be capable of successfully measuring signigicant changes or delays in the development of cognitive and neurological function as a result of long-term phenobarbital or other anticonvulsant therapy.

The DNB has extended a major effort during this fiscal year to meet the objectives of the Comprehensive Plan for Analysis and Interpretation of NINCDS Collaborative Perinatal Project (NCPP) Data. Two major areas of the Comprehensive Plan were completed during the year: a book dealing with communicative disorders in NCPP children was published and a book on minimal brain dysfunction is in press. Also, during the year a total of 29 papers were published or are in press; these papers are cited in the body of the report. As the NINCDS will soon complete its use of the Collaborative Perinatal Project data, an RFP has been issued which proposes to contract for the management of the microfilm and computer tape files as a national data resource for bona fide biomedical/behavioral researchers.

Other activities of the DNB include primary responsibility for administering the Privacy Act within the NINCDS, conducting reviews of NINCDS research contract proposals to assure the protection of human subjects, and committee participation in planning the equal employment opportunity contract compliance program of the NIH.

II. NINCDS COLLABORATIVE PERINATAL PROJECT

The NINCDS Collaborative Perinatal Project (NCPP) is a longitudinal multidisciplinary research effort which seeks leads to the etiologies of cerebral palsy, mental retardation, learning disorders, congenital malformations, minimal brain dysfunction, convulsive disorders, visual abnormality, and communicative disorders through studies which relate the events, conditions, and abnormalities of pregnancy, labor and delivery to the neurological and mental status of the children of these pregnancies as the child grows and develops. Data collection is complete, and data analysis is now complete in most areas of study. The Comprehensive Plan for Analysis and Interpretation of Collaborative Perinatal Project Data provided the framework for this effort. The Comprehensive Plan includes 10 primary and 10 secondary areas of study as listed below. The major emphasis of the project has shifted almost entirely to data interpretation and the writing of reports for publication of the NCPP research findings. Significant publications stemming from the Comprehensive Plan are noted in the listing below if the study area is concluded, in the individual contract narratives or project reports, and some are highlighted in the General Summary.

A. The ten primary areas are:

Cerebral Palsy (Project No. Z01 NS 02059-08 DNB)

Mental Retardation (Project No. Z01 NS 02106-07 DNB)

Communicative Disorders (Completed in FY'80 - See Lassman, F.M., Fisch, R.O., Vetter, D.K., and LaBenz, E.S.: Early Correlates of Speech, Language and Hearing. Edited by LaBenz, P.J., and LaBenz, E.S. Littleton, Massachusetts, PSG Publishing Company, 1980, 858 pp.) (Contract No. N01 NS 4-2326)

Visual Abnormality (Project No. Z01 NS 02107-07 DNB)

Convulsive Disorders (Project Nos. Z01 NS 02058-08 DNB &
Z01 NS 02234-05 DNB)

Learning Disorders (Project No. Z01 NS 02108-07 DNB)

Minimal Brain Dysfunction (Completed in FY'80 - See Nichols, P.L., and Chen, T.C.: Minimal Brain Dysfunction: A Prospective Study. Hillsdale, N.J., Lawrence Erlbaum Associates, in press) (Project No. Z01 NS 02062-08 DNB)

Congenital Malformations (Project No. Z01 NS 02109-07 DNB)

Birthweight-Gestational Age Relationships (Project No.
Z01 NS 02060-08 DNB)

Neuropathology, General Pathology and Placentology (Contract Nos.
N01-NS-3-2312 & N01-NS-7-2376)

B. The ten secondary areas are:

Toxemia (Completed in FY'77 - See Friedman, E.A., and Neff, R.K.: Pregnancy Hypertension. Littleton, Mass., PSG Publishing Co., Inc., 1977, 258 pp.)

Maternal Infection during Pregnancy (See report by Infectious Diseases Branch, NINCDS)

Neonatal Hyperbilirubinemia (Project No. Z01-NS-02112-07 DNB)

Maternal Anesthesia-analgesia during Labor and Delivery (Contract No. N01-NS-8-2381, and Project No. Z01 NS 02169-06 DNB)

Four-Year IQ (Completed in FY'75 - See Broman, S.H., Nichols, P.L, and Kennedy, W.A.: (Preschool I.Q.: Prenatal and Early Developmental Correlates. Hillsdale, N.J., Lawrence Erlbaum Associates, distributor, Halsted Press, John Wiley & Sons, N. Y., 1975, 360 pp.)

Physical Growth and Development (Contract No. N01-NS-5-2308)

Twins (Project Nos. Z01 NS 02109-07 DNB and Z01 NS 02332-03 DNB)

Genetic and Socio-economic Factors (Project Z01 NS 01857-11 DNB, Z01 NS 01754-12 DNB, and Z01 NS 01274-16 DNB)

Drugs taken during Pregnancy (Completed in FY'77 - See Heinonen, O.P., Slone, D., and Shapiro, S: Birth Defects and Drugs in Pregnancy. Littleton, Mass., Publishing Sciences Group, Inc., 1977, 516 pp.)

Labor and Delivery (Contract No. N01-NS-8-2381)

III. SUMMARY OF WORK IN PROGRESS:

Section on Cerebral Palsy and Other Motor Disorders

In the cerebral palsy area a univariate screen has been reevaluating maternal and pediatric conditions most strongly associated with cerebral palsy. Initial regression analyses have been run. Cerebral palsy at 7 years is found more frequently in boys than girls, and among whites than blacks. Twelve per cent of cerebral palsy is apparently caused by events occurring after the first month of life, most often infection or trauma. Clearly handicapping cerebral palsy was present at age 7 in 22-33/10,000 children, the range being related to race and sex. Studies have been completed and published demonstrating the relationship of birthweight and gestational age to cerebral palsy. Within each birthweight and gestational age group examined white males were at highest risk of cerebral palsy. Although low birthweight and immaturity are risk factors for cerebral palsy, 59% of cerebral palsy and 69% of the cerebral palsy other than spastic diplegia occurred in infants of term weight and full (37 or more weeks) gestational age. Studies are now in manuscript form concerning low Apgar scores at 10, 15, and 20 minutes as predictors of long-term neurological morbidity, and early recognition of infants at "high-risk" for cerebral palsy. Associated handicaps have been investigated in children with cerebral palsy, and natural history described in children who "outgrew" cerebral palsy, i.e., those children who showed signs of cerebral palsy at an earlier age but at the 7-year examination were free of motor handicap. The major multivariate analyses relating to the antecedents of cerebral palsy are now in progress.

In the convulsive disorders area, major findings are that approximately one in 20 children (57/1000) at age seven years have had at least one seizure. About 1/10 of that number (4.8/1000) had active epilepsy by the age of seven. In the NCPP population, epilepsy in childhood is approximately equal in prevalence in blacks and whites. Two-thirds of children who had seizures between one month and seven years of age had febrile seizures only. Data on prevalence of specific seizure disorders in early childhood are now available and were presented at an international meeting on child neurology. Approximately a quarter of children with epilepsy in early childhood have another major neurological handicap -- either mental retardation or cerebral palsy, or both. Seizures occurring in the first months of life were associated with a relatively high rate of death or subsequent disability including cerebral palsy. Neonatal seizures were found to be a major marker of risk for subsequent neurologic morbidity, and neonatal seizures in full term infants with very low Apgar scores appeared to be an important predictor of chronic neurologic disability. Low birthweight and short gestation were not important risk factors for seizure disorders in children who did not also have cerebral palsy. The major multivariate analyses concerning the antecedents of convulsive disorders are now in progress.

A study of febrile seizures has been a major focus of the convulsive disorders area. Of 1706 children with febrile seizures followed to the age of 7 years, 2% had become epileptic by the age of 7 and another 1% had had at least one nonfebrile seizure not meeting the definition of epilepsy. Comparison of 431 children who have had febrile seizures only with their seizure-free siblings indicates that febrile seizures do not "cost" the child a loss in IQ or increased vulnerability to learning disorders. Three risk factors were identified which served to mark children at special risk of subsequent epilepsy among children who have had febrile seizures. The best predictor of recurrence of febrile seizures was early age of onset.

Current activities on febrile seizures include several invited chapters for books, a paper relating sample selection to observed outcome in febrile seizures, and an NIH Consensus Development Conference on Long-term Management of Children with Febrile Seizures. Results of the consensus meeting, held this fiscal year, are being prepared for publication in professional journals, and the papers are being edited for a monograph. Results of the meeting are available in a DHHS publication Febrile Seizures, a National Institutes of Health Consensus Development Conference Summary, Vol. 3, No. 2. A pilot study of cognitive and behavioral effects of anticonvulsant medication in children with febrile seizures is underway, and a major study planned which will evaluate the effects of medications and of recurrent seizures. A program announcement is planned to invite studies on the effects of anticonvulsant agents on the developing nervous system.

Section on Mental Retardation and Learning Disorders

In the mental retardation area, all major statistical analyses of the data are completed, and a monograph is in preparation. Classification of the severely retarded children shows that 25% of whites and 50% of blacks had no major genetic or neurological abnormality. Perinatal risk factors for the severely retarded group as a whole include Down's syndrome, major CNS malformations, neonatal seizures and clinical signs of perinatal hypoxia. For the subgroup of severely retarded with unknown etiology, perinatal risk factors include non-CNS malformations, peripheral nerve abnormalities, signs of hypoxia, and maternal urinary tract infection during pregnancy. A report on teenage pregnancy as a risk factor for poor cognitive outcome has been published.

In the learning disorders area, a second draft of the monograph is in preparation. The findings show that among children with average IQ scores and below average achievement test scores, socioeconomic status and family size were better predictors of unexpected school failure than were indices of physical or neurological status. Beginning in the preschool period, low achievers had higher frequencies of cognitive and behavioral problems, and neurological soft signs than did their IQ-matched controls. Hyperactive low achievers had an increased frequency of obstetrical complications. Sex differences were found in precursors as well as in the incidence of unexpected academic failure.

The final report of the study of symptoms of minimal brain dysfunction is in press. Antecedents of hyperkinetic-impulsive behavior included maternal smoking during pregnancy, delayed motor development at 1 year, absent father, and affected siblings. Learning difficulties were associated with low socioeconomic status, large families, frequent family moves, and affected siblings. Among the early antecedents of neurological "soft signs" were low Bayley motor score at 8 months, delayed motor development and small head size at 1 year, and again, affected siblings. All three MBD symptoms diagnosed at age 7 were related to behavioral, cognitive, and motor problems at age 4.

Analyses in the area of obstetric medication and later physical and cognitive development in a cohort of normal births are near completion, and a report is in preparation. The findings suggest that inhalants are associated with deficits in psychomotor and neuromotor functioning in infancy, and that some drugs given during labor and delivery are associated with lower scores on cognitive tasks at later ages.

Section on Birth Defects and Genetic Disorders

Two parts of the 11-part program plan for the comprehensive analysis of congenital malformations remain to be completed: the analysis of multiple malformations, and the analysis of the 7-year malformations. Though lack of computer programming help has slowed the pace of these analyses considerably, substantial progress has been made. Findings from the latter analysis indicate that children lost to study did not have a higher frequency of malformations than those maintained in the sample. About 19% of children followed to age 7 years had malformations, representing an increase of 4% from 1 year which is mainly due to newly identified eye, mouth and genitourinary malformations, and tumors.

Studies of twins are in progress to assess and interpret the influence of maternal, socioeconomic, neonatal, medical and other environmental factors on survival, growth and development, and on abnormal outcome of NCPP twins.

An in-depth study of external ear malformations has been completed and has been published in monograph form; similar studies of neural tube defects, microcephaly, pyloric stenosis and congenital heart defects are in progress.

Plans are being developed for new initiatives to encourage special studies of molecular mechanisms which operate during embryonic development of the CNS, and of the factors which disrupt these mechanisms, resulting in CNS defects. In particular, a conscious effort is being made to interest investigators in the early abortion fetuses which are still available in Japan.

Section on Autism and Behavioral Disorders

Studies have continued on the 14 autistic children identified in the NCPP. Earlier published work on this sample reported increased vaginal bleeding during the second trimester of pregnancy. Cord blood samples have been examined for presence of certain antiviral antibodies but no significant results were found. Tabulations have been prepared on the autistic children and controls for a series of findings from the neonatal neurological examination, the 8-month developmental examination, and the 1-year neurological examination in an attempt to identify predictive signs of autism. A manuscript is being prepared.

Proceedings of the Workshop on the Neurobiological Basis of Autism have been published as NINCDS Monograph No. 23. The volume reports on the presentations and discussions of the following topics: definition, neuropsychology, language, neurophysiology (vestibular and evoked potential research), and neurochemistry. The recruitment effort for the Section Head for the Autism and Behavioral Disorders Section identified a qualified candidate, who has been extended a formal offer for the position.

Collaborative Perinatal Section

The contracted study of communicative disorders is complete and a book published following extensive editing including production of a detailed index (27 book pages). Lassman, F.M., Fisch, R.O., Vetter, D.K., and LaBenz, E.S.: Early Correlates of Speech, Language and Hearing. Edited by Labenz, P.J., and LaBenz, E.S. Littleton, Massachusetts, PSG Publishing Company, 1980, 858 pp.

In the area of visual abnormality data analysès are complete and a final report is in preparation which will include computer generated tabulations from the study.

The Birthweight-Gestational Age Relationships (Prematurity) analyses have been completed, including re-runs of parts of Phase II and all of Phase III. A monograph is in preparation, with figures and tables essentially completed.

The two contracted analyses in the area of pathology, one for neuropathology and one for general and placental pathology are complete. In the neuropathology segment, work on the manuscript of the monograph continued during the fiscal year. In the general and placental pathology segment, reports during this fiscal year included studies of weight gain and pregnancy outcome, of coitus during pregnancy and associated amniotic fluid infections, and of causes and consequences of premature rupture of membranes.

The contracted study of toxemia of pregnancy is complete and a book published. Friedman, E.A. and Neff, R.K.: Pregnancy Hypertension. Littleton, Mass., PSG Publishing Company, Inc., 1977, 258 pp.

A book describing the characteristics of NCPP children during their first year has been published. Hardy, J.B., Drage, J.S., and Jackson, E.C.: The First Year of Life. Baltimore, Md., The Johns Hopkins University Press, 1979, 336 pp.

Studies on neonatal hyperbilirubinemia have suggested that neurological impairment at one year may be associated with neonatal serum bilirubin level below 20 mg.%. Interpretation of an analysis of neonatal bilirubin levels and seven year outcomes identified additional analyses needed to complete this study. A manuscript is in preparation.

Work has continued under contract on the Comprehensive Study of Labor and Delivery Effects on Offspring. Emphasis was on Phase V of the workscope which involved assessment of a large series of variables related to delivery practices and how these factors affected the fetus and the surviving child. Incomplete portions of Phases II, III and IV were also pursued. These included a study of drugs given during labor and delivery which produced both adverse and favorable (protective) outcome but definitive interpretation is confounded at this stage of the analyses. Striking data were evolved with regard to forceps delivery; the adverse effect of midforceps was clearly confirmed.

Work and reporting of results in the area of physical growth continued this fiscal year. A final comprehensive report is expected.

The contracted screening study of maternal drug ingestion is complete and a book published. Heinonen, O.P., Slone, D., and Shapiro, S.: Birth Defects and Drugs in Pregnancy. Littleton, Mass., Publishing Sciences Group, Inc., 1977, 516 pp.

IV. HIGHLIGHTS OF FINDINGS FROM THE NCPP

Findings from the NCPP have had and are continuing to have an impact on national health policy. It seems appropriate to highlight some of the more important contributions to date.

The concern over the potential dangers of alcohol consumption by a pregnant woman to her unborn fetus was highlighted in a notice in the Federal Register, Vol. 44, No. 29 - Friday, February 9, 1979. In that notice, the Department of the Treasury recommended a public awareness campaign to educate the public about the nature of the problem. The existence of the "fetal alcohol syndrome," a constellation of congenital anomalies thought to appear in offspring of chronic alcoholic women, was confirmed, prospectively, using data on women and children enrolled in the NCPP. The appearance of the paper in the Lancet (Jones, K.L., Smith, D.W., Streissguth, A.P., and Myrianthopoulos, N.C.: Outcome in offspring of chronic alcoholic women. Lancet I: 1076-1078, 1974) stimulated additional research and subsequent governmental and public concern over this issue.

The work by Dr. Dennis Slone and his colleagues at Boston University, completed under contract with the NINCDS, developed an association between cardiovascular birth defects and female hormones taken by the mother during pregnancy. The paper appearing in the New England Journal of Medicine (Heinonen, O.P., Slone, D., Monson, R.R., Hook, E.B., and Shapiro, S.: Cardiovascular birth defects and antenatal exposure to female sex hormones. N. Engl. J. Med. 296: 67-70, 1977) led directly to new Federal drug labeling requirements for this class of drugs as published in the Federal Register, Vol. 43, No. 199 on Friday, October 19, 1978. The paper is cited in the Federal Register.

Febrile seizures affect 3.5 percent of all children born in the United States. The study by Drs. Karin Nelson and Jonas Ellenberg, of the

NINCDS, (Nelson, K.B and Ellenberg, J.H.: Prognosis in children with febrile seizures. Pediatrics 61: 720-727, 1978) presented data concerning the degree of risk of future epilepsy in children experiencing febrile seizures. In children with a prior neurological abnormality and one or more other risk factors (family history of epilepsy, first seizure type), the risk was high, but for children with no prior abnormality, no history of epilepsy in the immediate family, and when the first seizure was of a pure (not complex) type, the risk of subsequent epilepsy was quite low. This low risk group included 60% of children with febrile seizures and the authors state that this group would not seem an appropriate target population for chronic treatment aimed at the prevention of afebrile seizures. Another 34% of children had only one risk factor and they experienced little increase in risk of epilepsy. The NIH held a Consensus Development Conference during this fiscal year which attempted to resolve the issue of management of febrile seizures in current medical practice. Findings from the NCPP were prominently featured in the final report emanating from the conference.

In 1979 a report of the Surgeon General on Smoking and Health was released. Chapter 8 is on Pregnancy and Infant Health and there are six references to publications from the NCPP that significantly contribute to the report's conclusion that smoking during pregnancy is deleterious to the baby during intrauterine life.

Other significant findings from the NCPP include evidence that there is prior neonatal brain dysfunction in sudden infant death syndrome (Naeye, R.L., Ladis, B., and Drage, J.S.: Sudden infant death syndrome: a prospective study. Am. J. Dis. Child. 130: 1207-1210, 1976), that only one third of congenital malformations are detected at birth (Myrianthopoulos, N.C. and Chung, C.S.: Congenital malformations in singletons. Epidemiologic survey. Report from the Collaborative Perinatal Project. Birth Defects, Orig. Art. Series, Vol. X, No. 11, 1974), that bilirubin is neurotoxic at intermediate levels (Scheidt, P.C., Mellits, E.D., Hardy, J.B., Drage, J.S., and Boggs, T.R.: Toxicity to bilirubin in neonates: infant development during the first year in relation to maximum neonatal serum bilirubin concentration. J. Pediatr. 91: 212-297, 1977.), and that frequency of coitus during pregnancy may be implicated in the etiology of amniotic fluid infections. (Naeye, R.L.: Coitus and associated amniotic-fluid infections. N. Engl. J. Med. 301: 1198-1200, 1979.)

V. CONTRACTS, GRANTS, AND COOPERATIVE AGREEMENTS:

An RFP was released on July 28, 1980 which seeks offers to establish a system making NCPP data available for use in research. Because the DNB is completing its use of the NCPP Data, the intent of this proposed contract is to seek the best qualified organization to manage and promote the NCPP data, to honor requests from qualified researchers who wish to use NCPP data in their research, and to assist researchers in using the data. The contract mechanism is being considered for selected studies of febrile seizures and effects of anticonvulsant medication on behavior and cognition, based on recommendations of the

NIH Consensus Development Conference. The DNB plans to seek renewal for a fourth and final year of the contract to study labor and delivery; the original analysis plan called for a four year effort.

The DNB has been assigned responsibilities in the area of grants administration. During the fiscal year the DNB, representing the NINCDS, significantly contributed to the development and publication on May 16, 1980 of a program announcement encouraging the submission of research grant applications in the area of Reye's Syndrome, a clinically important childhood encephalopathy, increasingly recognized as a major health problem. The program announcement is being co-sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Child Health and Human Development (NICHD), and the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD). Program announcements in the areas of the neurobiology of childhood autism and neonatal brain disorders are under development. DNB professional staff is receiving training in grants administration in preparation for assuming these new responsibilities. Approximately 150 ongoing research grants classified as Disorders of Early Life are in the process of being transferred to the DNB from the Office of the Director, NDP.

The cooperative agreement is a new instrument for research support which is under consideration for use by the DNB in selected research efforts in which direct participation by DNB staff in the research is desirable.

VI. SUPPORT FUNCTIONS:

The Unit for Data Collection is responsible for maintaining the NINCDS Collaborative Project files and the microfilming of the records in accordance with a system designed to facilitate data retrieval. During the fiscal year major efforts were concentrated on preparation of records for microfilming, editing microfilm, supplying records to the DNB professional staff, outside investigators and consultants, providing research assistance to ongoing studies and preparing NINCDS microfilmed records for Federal Storage.

The Unit for Production of Data Analysis has as its basic mission the processing and storage by digital computer of the medical research data collected by the NCPP. The Unit provides data processing support to the researchers in their analysis of the data. The major research files have been completed and in-depth statistical analysis has been performed. By the end of the fiscal year, approximately 40 requests for analysis of data will have been completed.

The following systems are now in operation:

1) A financial system that accounts for all computer funds spent by the Branch.

2) An automated bibliography of all publications emanating from the NCPP.

A system to create an index of all variables found in the NCPP Master File, Variable File and Peripheral Files is under study.

VII. OUTSIDE REQUESTS FOR NCPP DATA:

It is the policy of the DNB to encourage the appropriate use of the NCPP data by providing advice, data, and assistance to qualified biomedical and behavioral researchers who wish to utilize these data in their research. A policy statement has been developed which specifies the requirements to be met by a researcher who wishes to utilize NCPP data supplied by the DNB. The policy statement was formally approved by the Director, NINCDS and is available on request.

Requests for NCPP data to initiate new studies or to obtain specific information from NCPP data files continue to be received from researchers who receive their support from agencies and institutions other than the NINCDS. New requests this fiscal year include:

Child and Family Research Branch, National Institute of Child Health and Human Development, on predictors and outcomes of cesarean delivery; New England Regional Primate Center, Harvard Medical School, on sex hormones given during pregnancy; the University of Tennessee Medical School on selected follow-up of NCPP children in the Tennessee sample; Massachusetts General Hospital and Harvard Medical School on effects of maternal phenylketonuria on pregnancy and offspring; Department of Preventitive Medicine and Community Health, University of Texas Medical Branch, Galveston, on relationships between exposure to chemical pollution (pesticides) and adverse pregnancy outcomes; Division of Pediatric Cardiology, University of Maryland School of Medicine, on seasonality of cardiac arrhythmias; Department of Pediatrics, University of Colorado Medical Center, Denver, on genetics of placental aryl hydrocarbon hydroxylase induced by cigarette smoke.

VIII. ADDITIONAL ACTIVITIES

The Office of the Chief, DNB, continues as the NINCDS focal point for implementation of the Privacy Act. The Chief, DNB, continues to serve as NINCDS Privacy Act Coordinator. Activities for this fiscal year include the following: (1) advice to NINCDS personnel regarding Privacy matters; (2) determination of the applicability of the Privacy Act to each new NINCDS contract involving human subjects; (3) required quarterly and annual reports prepared and submitted to the NIH Privacy Act Coordinator; (4) reviewing requests for access to or amendment of grant records; (5) attending orientation sessions regarding changing regulations in implementation of the Act; and (6) revising NINCDS System Notices to comply with new regulations.

The Office of the Chief, DNB, continues to administer the Clinical Research Panel, NINCDS Contract Review for the Protection of Human Subjects, and the Chief, DNB, serves as Chairman. This panel has the responsibility for reviewing NINCDS contracts for adherence to DHHS and NIH rules and regulations regarding the protection of human subjects in research and recommending approval or disaproval to the Director, NINCDS. During the first nine months of the fiscal year, 9 new contract proposals were reviewed by the Panel, and 2 renewals were processed.

The Chief, DNB, and the Staff Assistant to the Chief, DNB, are members of the NIH Contract Compliance Committee for Project Officers, chaired by the Contract Compliance Coordinator, NIH. This committee had as its charge the development of a questionnaire to be administered by project officers to principal investigators/project directors on NIH contracts for the purpose of increasing awareness of and monitoring compliance with Federal requirements for Equal Employment Opportunity. During this fiscal year a pilot course for NIH Project Officers was developed and tested and formal training initiated NIH wide, and use of the questionnaire, in the field, commenced.

CONTRACT NARRATIVE
Developmental Neurology Branch, NDP, NINCDS
Office of the Chief
October 1, 1979 through September 30, 1980

CHILDREN'S HOSPITAL MEDICAL CENTER, BOSTON, MASSACHUSETTS (N01-NS-3-2312)

Title: Combined Neuropathologic and Epidemiologic Study

Contractor's Project Director: Floyd H. Gilles, M.D.

Current Annual Level: $ 0.00

Objectives: The contract will analyze the neuropathology collection of the NINCDS Collaborative Perinatal Project (NCPP). An estimate of the quality of the material and a catalogue of gross brain abnormalities will be prepared. Plots of fetal brain weight of grossly normal brains against estimated gestational age, utilizing a Gompertz function, will be made and an analysis will be made relating events of pregnancy, labor, and delivery. A comparison will be made of rate of brain weight acquisition in utero to rate of brain weight acquisition after birth as a function of total (gestational plus survival) age. A study will be made of intracranial hemorrhage including topography of hemorrhage. A study will be done on the risk factors associated with perinatal telencephalic leucoencephalopathy. A study of cerebral necrosis is to be completed which would include criteria of necrosis in the perinatal brain, and an evaluation of selected risk factors in relation to subclassification of neuronal and white matter necrosis.

Major Findings: Review and classification of pathology material are complete. Data analysis is complete and a monograph report is in preparation.

Course of Contract: June 1, 1973 through December 31, 1976. The contract is terminated; extra time is being allowed to complete and publish the monograph report.

CONTRACT NARRATIVE
Developmental Neurology Branch, NDP, NINCDS
Office of the Chief
October 1, 1979 through September 30, 1980

UNIVERSITY OF MINNESOTA (N01-NS-4-2326)

Title: Analysis of Speech, Language and Hearing Deficits to Facilitate Prevention, Diagnosis and Treatment

Contractor's Project Directors: Frank M. Lassman, Ph.D., and
Robert O. Fisch, M.D.

Current Annual Level: None

Objectives: Speech, language and hearing (SLH) data were collected as part of the Collaborative Perinatal Project (NCPP) of the National Institute of Neurological and Communicative Disorders and Stroke. Populations were sampled at twelve medical institutions located largely in eastern and southern states. Data from SLH examinations administered at 3YR and 8YR were analyzed for interrelationships and for associations with findings in other areas of the NCPP study. These include variables relating to pregnancy, labor and delivery, family characteristics and the physical, mental and behavioral characteristics of the children. Relationships among the variables were studied to provide clues to the etiology of communicative disorders, and to uncover findings which might be clinically applicable as well as predictive of outcome.

The SLH data were examined for quality as it pertains to availability of the data, reasonableness of values and stability of findings. Examiner variability was evaluated on the basis of test-retest results obtained from the NCPP quality control program. The quality of most SLH variables appeared satisfactory.

Major Findings: Relationships between SLH outcome and selected NCPP variables included the following: 1. Race, sex, SEI and IQ contributed most to predicting the 8YR language indexes; 2. Failure on 8-month Bayley vocalization items increased by 2 to 3 times the risk of later poor language performance; 3. Single children performed better than those with siblings; 4. Written communication (reading, writing, spelling) showed systematic improvement with increasing IQ, SEI and education of the parents; 5. Failure of the 3YR Pure Tone Hearing Screen was predictive of loss in hearing sensitivity at 8 YR; 6. Higher relative risks for sensorineural hearing loss in children was suggested for certain drugs administered to mothers during pregnancy; and 7. Variables indicative of socioeconomic level have the strongest relationship to SLH outcome at 8YR.

Course of Contract: June 29, 1974 through June 28, 1976. Extension of time was required for completion, but with no additional funding. Contract expired March 31, 1977.

Contract No. N01-NS-4-2326

Publication: Lassman, F.M., Fisch, R.O., Vetter, D.K., and LaBenz, E.S.: Early Correlates of Speech, Language and Hearing. Edited by LaBenz, P.J., and LaBenz, E.S. Littleton, Mass., PSG Publishing Company, 1980, 858 pp.

CONTRACT NARRATIVE
Developmental Neurology Branch, NDP, NINCDS
Office of the Chief
October 1, 1979 through September 30, 1980

UNIVERSITY OF MICHIGAN (NO1 NS 5-2308)

TITLE: Physical Growth Analysis

Contractor's Project Director: Stanley M. Garn, Ph.D.

Current Annual Level: $ 00.00

Objectives: To develop the physical growth measurement data on the 50,000 children examined within the framework of the NINCDS Collaborative Perinatal Project (NCPP). Specifically:

1. Develop for body weight, length, chest circumference and head circumference, a set of tabular, percentile, normative tables of (a) size-for-age, (b) increments of size for age-interval, (c) size-for-size for age and size for gestation length for whites, blacks and Puerto Ricans separately and for boys and girls separately. This set of tables is largely intended as a reference document for the NINCDS Collaborative Perinatal Project.

2. Develop a set of summary tabulations and reports, directed to the major pediatric and growth-related users, complete with narrative and graphs, with the purpose of providing in the professional literature both an account of major substantive findings, and an in-the-literature account of the major data based along lines described in 1, but simplified as necessary.

3. To correlate the incidence and prevalence of dental and facial abnormalities with neurological defects, congenital abnormalities and other disorders of childhood.

Major Findings: Findings are reflected in publications to date.

Significance to the Program: The findings support previous study findings and are important to the pediatric community as well as to physical anthropologists in that they represent results from the largest longitudinal data base yet studied in the U.S.

Course of Contract: Terminated April 30, 1980. The planned series of publications will be completed and a final, comprehensive report is expected.

Publications:

Garn, S.M., Hoff, K., and McCabe, K.D.: Is there nutritional mediation of the "smoking effect" on the fetus. Am. J. Clin. Nutr. 32:1181-1184, 1979.

Garn, S.M., Osborne, R.H., and McCabe, K.D.: The effect of prenatal factors on crown dimensions. Am. J. Phys. Anthrop. 51:665-678, 1979.

Garn, S.M., Shaw, H.A., and McCabe, K.D.: Pregnant? No ifs, ands or butts. Resident & Staff Physician, Sept., 1979, pp 152-162.

Garn, S.M., and Keating, M.T.: Effect of various prenatal determinants on size and growth through seven years. Ecol. Food & Nutr. 9:109-112, 1980.

Garn. S.M.: Human Growth. Ann. Rev. Anthropol., in press.

CONTRACT NARRATIVE
Developmental Neurology Branch, NDP, NINCDS
Office of the Chief
October 1, 1979 through September 30, 1980

THE PENNSYLVANIA STATE UNIVERSITY, UNIVERSITY PARK, PA. (N01-NS-7-2376)

Title: Analysis of General and Placental Pathology Data

Contractor's Project Director: Richard L. Naeye, M.D.

Current Annual Level: $ 0.00

Objectives: The objectives of the extension of the contract were (1) to complete the determination of the effects of smoking on the fetus, (2) a further explanation of the relationship between prepregnancy weight for height and placental growth as related to fetal growth and pregnancy outcome, and (3) a determination if selected factors thus far examined have an independent influence on long term psychomotor development in NCPP children.

Major Findings: Findings are reflected in publications to date.

Course of Contract: The contract terminated July 31, 1979; extra time is allowed to complete the planned series of publications, and a final, comprehensive, report is expected.

Publications:

Naeye, R.L.: Weight gain and the outcome of pregnancy. *Am. J. Obstet. Gynecol.* 135:3-9, 1979.

Naeye, R.L.: The duration of maternal cigarette smoking, fetal and placental disorders. *Early Hum. Dev.* 3:229-237, 1979.

Naeye, R.L.: Coitus and associated amniotic-fluid infections. *N. Engl. J. Med.* 301:1198-1200, 1979.

Naeye, R.L.: Causes of fetal and neonatal mortality by race in a selected U.S. population. *Am. J. Public Health* 69:857-861, 1979.

Naeye, R.L.: Causes and consequences of premature rupture of fetal membranes. *The Lancet* I:192-194, 1980.

Naeye, R.L.: Seasonal variations in coitus and other risk factors, and the outcome of pregnancy. *Early Hum. Dev.* 4:61-68, 1980.

CONTRACT NARRATIVE
Developmental Neurology Branch, NDP, NINCDS
Office of the Chief
October 1, 1979 through September 30, 1980

CHILDREN'S HOSPITAL MEDICAL CENTER, BOSTON, MASSACHUSETTS: (N01-NS-7-2377)

TITLE: A Prospective Cohort Epidemiologic Study of Learning Handicaps in Children Attending School

Contractor's Project Director: Alan Leviton, M.D.

Current Annual Level: $97,627.00

Objectives: Conduct analyses of antecedents of school behavior and school achievement at age 9 in an identified sample of children in the Boston component of the NINCDS Collaborative Perinatal Project (NCPP) for the purpose of identifying risk factors for learning disorders.

Major Findings: Five learning handicaps in boys and six in girls have been identified as outcomes of interest. Antecedents are being analysed by epoch--e.g.--pre-pregnancy, pregnancy, delivery, early postnatal. An interactive multiple logistic regression procedure is being used to analyse the data. Risk factors for learning handicaps include low family income, large family size, prior abortions, and some complications of pregnancy.

Course of Contract: September 30, 1977 through November 14, 1980.

CONTRACT NARRATIVE
Developmental Neurology Branch, NDP, NINCDS
Office of the Chief
October 1, 1979 through September 30, 1980

BETH ISRAEL HOSPITAL, BOSTON, MASSACHUSETTS (N01-NS-8-2381)

Title: Comprehensive Study of Labor and Delivery Effects on Offspring

Contractor's Project Director: Emanuel A. Friedman, M.D.

Current Annual Level: No FY-80 funds

Objectives: The objectives are (1) to determine the effects on the fetus and the surviving infant of clinically definable labor factors, labor disorders and the spectrum of delivery procedures, and thus to identify and quantitate the specific risk factors in labor and delivery that contribute to perinatal mortality and to the development of long-term neurological and developmental disorders in children, and (2) to determine relationships between the various types of maternal anesthesia-analgesia and development of the child; specifically, to examine in detail the time-dose relationships and drugs used in combination during the course of labor and delivery, in relation to long-term neurological outcome in the child.

Major Findings: Work on the contract has progressed and the required report following Phase V has been received. The objectives of Phase V involved assessment of a large series of variables related to delivery practices and how these factors affected the fetus and surviving child. This included (a) determining the categories and distributions of the delivery variables, and (b) studying the outcome effects of these variables. Progress also continued in completing areas of additional work needed on Phases II, III, and IV. Work on Phase VI is progressing. The initial analyses showed striking data regarding forceps delivery and outcome. The adverse effect of midforceps is clearly confirmed, especially as related to neonatal death, neonatal depression reflected low Apgar scores at 5 minutes of age, and 4-year and 7-year IQ results in children of nulliparas. The same is seen in multiparas with the single exception of the 4-year IQ data. Even low midforceps, done with the fetal skull on the perineal floor but with the sagittal suture not in the anteroposterior diameter of the pelvis, carries uniformly poor long-term IQ results in both nulliparas and multiparas.

Course of Contract: March 13, 1978 through March 12, 1982. A fourth year was requested in the original proposal.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 01163-18 DNB

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Selected Maternal Risk Factors and Congenital Cardiovascular Anomalies

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Bajda	Medical Consultant	DNB, NINCDS
OTHER:	A. Naylor	Research Geneticist	DNB, NINCDS

COOPERATING UNITS (if any)

LAB/BRANCH
Developmental Neurology Branch

SECTION
Birth Defects and Genetic Disorders Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.0	0.5

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study, using data from the NINCDS Collaborative Perinatal Project, investigates the relation of selected factors which may affect the mothers during pregnancy, and possibly cause congenital heart defects in the children. Observations on about 47,000 pregnancy records provide case and control data for analysis. Some 486 children have been identified as having definite congenital cardiac anomalies. These include cardiac conditions which are part of known syndromes but exclude children suspected of having ventricular septal defect who are reported without cardiac defect at the 1-year examination and thereafter. Pre-selected maternal risk factors noted in the pregnancy records for the mothers of 392 children with definitely defined congenital heart anomalies are compared with control data matched for maternal age, race, date of LMP, and geographical location (institution).

PHS-6040
(Rev. 10-76)

Project Description:

Objectives: Primary objective is the identification of maternal/environmental conditions causing pregnancy outcome at risk for congenital cardiac anomalies. Another objective is delineation of the course of congenital hearts from birth through 7 years in terms of specific diagnosis and condition outcome.

Methodology: a) Selection of cases with cardiovascular anomalies by computer printout of codes from periodic "summary of diagnosis" followed by detailed review of records for verifying specific diagnosis. b) Development of numerical codes of cardiac diagnosis for computer input. c) Development of a maternal data protocol coding items not available in the computer data bank. d) Using epidemiologic skills for identifying significant maternal factors impacting on pregnancy outcome.

Major Findings: 1) The study population was further identified and defined. Preliminary reports in 1965 were skewed, being weighted with the more serious cardiacs identified early by autopsy and by undifferentiated syndrome cases. The epidemiological significance of carrying the analysis thru 7 years--particularly for congenital heart disease--can be appreciated when summaries (Ped 12) indicate 931 suspect and definite cardiacs at 1 year and 412 cardiacs thereafter thru 7 years (IDC 77)

Proposed Course: The study nears conclusion and publication.

Publications: None

Presentations: 3

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 01274-16 DNB

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Genetic Bases of Neonatal Reflexes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A.F. Naylor	Research Geneticist	DNB NINCDS
OTHER:	N.C. Myrianthopoulos	Research Geneticist	DNB NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Developmental Neurology Branch

SECTION

Birth Defects and Genetic Disorders Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.02	.02	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Neonatal reflexes (suck, rooting, palmar grasp, plantar grasp, Moro, etc.) are usually tested as signs of neurological and general well-being. A study has long been planned as to whether genetic variables may be sometimes responsible for absence of specific reflexes. A data file which contains genetic and background information has been enlarged to include data on neonatal reflexes so that the investigation can finally be carried out.

PHS-6040
(Rev. 10-76)

Project Description:

Objectives: To investigate the validity of regarding the suck, rooting and other neonatal reflexes as genetic entities.

Major Findings: A review of cases has led to criteria for accepting children as normal but lacking specific reflexes and rejecting those cases which are clearly abnormal. Appropriate codes, in the same format as malformations, have been included in the now completed Family Analysis File, which includes items on most possible abnormalities (physical or mental), background variables and relationships to other NCPP children.

Proposed Course: These variables will be analyzed familially by methods under development for all variables in the Family Analysis File. Special supplementary analyses will be carried out.

Publications: None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 01276-16 DNB

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Sequential Aspects of Occurrence of Spontaneous Abortion in Family Histories

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: A.F. Naylor	Research Geneticist	DNB NINCDS

COOPERATING UNITS (if any)

D. Warburton, College of Physicians and Surgeons at Columbia University

LAB/BRANCH
Developmental Neurology Branch

SECTION
Birth Defects and Genetic Disorders Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.02	.02	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this study has been to relate the risk of spontaneous abortion to maternal age and prior reproductive experience. Careful reconsideration of long available tabulations has shown convincingly that gravidity is a major correlate of spontaneous abortion and maternal age is of no importance.

PHS-6040
(Rev. 10-76)

Project Description:

Objectives: To relate the risk of spontaneous abortion to maternal age and prior reproductive experience. A special point under investigation is whether apparent age effects are explicable by a tendency for intrinsic habitual aborters to remain in the reproductive population longer in attempts to compensate for unsuccessful pregnancies. Also conditional risks have been estimated.

Proposed course: A paper arguing that age effects are real but laying emphasis on the decided importance of parity effects has already been published. This study is now terminated.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 01754-12 DNB

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)
Growth and Intellectual Development of Children from Interracial Matings

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A.F. Naylor	Research Geneticist	DNB NINCDS
OTHER:	N.C. Myrianthopoulos	Research Geneticist	DNB NINCDS

COOPERATING UNITS (if any)
L. Willerman, Department of Psychology, University of Texas at Austin

LAB/BRANCH
Developmental Neurology Branch

SECTION
Birth Defects and Genetic Disorders Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.01	.01	.00

CHECK APPROPRIATE BOX(ES)
☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A small subpopulation within NINCDS Collaborative Perinatal Project children has been identified as being of mixed black and white parentage. Within the interracial group of matings there is no evidence that genetic or socio-economic differences are related to race of mother (or father). Thus socio-psychological influences, presumably operating through mother-child interactions, can be examined indirectly. Two papers have been previously published which indicate that, although early childhood differences are wholly negligible, children of white mothers eventually develop positive intellectual differentials. A paper analyzing longitudinal differences in early growth rates has now been published.

PHS-6040
(Rev. 10-76)

Project Description:

Results of analyses of growth and intellectual development have been prepared for separate publication.

The conclusion reached in an initial publication in Science, that analyses of NCPP interracial matings for IQ data indicate that race of mother as a postnatal environmental indicator accounts for much of the black-white IQ differences, has been strengthened in a paper published last year. Analyses of Bayley Mental and Motor Scores, taken at 8 months, when maternal social influences will have had little effect show no differences between children of black/white and white/black matings. Also a more convincing demonstration has been made of lack of bias in genetic or socio-economic factors affecting four year IQ on the paternal side.

The physical development data have been re-analyzed to compare all properly selected NCPP interracial and monoracial matings. Hospital variation and other background factors were corrected for by multivariate regression. At birth children born to white mothers, whether by white or black fathers, are very similar in weight and length. Monoracial blacks are definitely smaller and interracials with black mothers may be intermediate in size (small numbers cloud the issue). At four months interracials with white mothers fall behind in weight (but catch up after one year), perhaps because of social stresses in the household. A paper laying out these points has been published by Social Biology.

Proposed Course: This project will be discontinued.

Publications: Naylor, A.F., and Willerman, L.: Physical Development of Interracial Children in the First Year. Soc. Biol. 26: 7-15, 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 01857 - 11 DNB

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

The Genetics of Intellectual and Motor Performance

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Sarah H. Broman	Acting Chief, MRLDS	DNB NINCDS
Other:	Paul L. Nichols	Research Psychologist	DNB NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Developmental Neurology Branch

SECTION
Mental Retardation and Learning Disorders Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: .15	PROFESSIONAL: .10	OTHER: .05

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Familial influences on tests of mental and motor performance at ages eight months and four and seven years were examined by comparing correlation coefficients among monozygotic twins, dizygotic twins, full siblings, half siblings, and cousins within race, sex, and social class groups. Similar correlations among physical measurements at these ages were also examined. A paper has been published on familial resemblance in infant mental development. The correlations between scores of twin and sibling pairs on the Stanford-Binet (age 4) and Wechsler (age 7) intelligence tests suggested a greater genetic influence than was found for infant test scores. This project is completed and a final paper is in preparation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02052-08 DNB

PERIOD COVERED

October 1, 1979 through September 30, 1980

TITLE OF PROJECT (80 characters or less)

The First Year of Life

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI.:	J. S. Drage	Chief	DNB, NINCDS
Other:	E. C. Jackson	formerly, Biostatistician	OBE, NINCDS

COOPERATING UNITS (if any)

J. B. Hardy, The Johns Hopkins University

LAB/BRANCH

Developmental Neurology Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0	0	0

CHECK APPROPRIATE BOX(ES)

X (a) HUMAN SUBJECTS X (b) HUMAN TISSUES ☐ (c) NEITHER

X (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

"The First Year of Life" is a volume reporting on the frequency distribution of a number of findings reported on NINCDS Collaborative Perinatal Project children during the first year of their lives. It includes information on birthweight-gestation distribution, bilirubin levels, age at hospital discharge, and distributions of various pathological findings detected during the nursery stay and during the first year of life. Of particular interest is the information regarding brain abnormality as detected during the nursery period. This volume is intended to serve as a general description of the Collaborative Project children during their first year of life and as a reference document for further in-depth studies. The document is published. Hardy, J.B., Drage, J.S., and Jackson, E.C.: The First Year of Life. Baltimore, The Johns Hopkins University Press, 1979, 336 pp.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF** **INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02058-08 DNB

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Convulsive Disorders Data Analysis Group

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	K.B. Nelson	Pediatric Neurologist	DNB NINCDS
PI:	J.H. Ellenberg	Mathematical Statistician	OBFS NINCDS

COOPERATING UNITS (if any)

Dr. J. Freeman, Johns Hopkins
Dr. K. Holden, Johns Hopkins

LAB/BRANCH
Developmental Neurology Branch

SECTION
Section on Cerebral Palsy and Other Motor Disorders

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.9	PROFESSIONAL: 0.6	OTHER: 0.3

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study examines the relationship between perinatal factors and the occurrence of seizure disorders in childhood in a large, prospectively studied population. In addition to the central question of etiology, it investigates frequency, prognosis, demographic characteristics, and a number of other aspects of these disorders. Univariate screen of maternal, obstetric, and pediatric risk factors, and demographic analysis, have been completed. File creation for multivariate analysis is now complete, and regression analyses are in progress. Selected topics of particular clinical relevance are under examination.

PHS-6040
(Rev. 10-76)

Objectives: To examine maternal characteristics, conditions of pregnancy, labor, delivery and the neonatal period, and illness and injuries of early childhood for their association with seizure disorders. To seek clinically useful indices for prediction, to evaluate clustering of other handicaps with convulsive disorders, and to examine the frequency of seizure disorders in the population of the NINCDS Collaborative Perinatal Project.

Methodology: The preliminary program to screen antecedent obstetric variables and early clinical manifestations with regard to their association with seizure disorder diagnoses has been completed. The analysis of demographic factors (e.g., institution, race, socioeconomic status, etc.) and their impact on the incidence and risk of seizure disorders is now available, and is in the process of assessment. A study into the natural history of seizure disorders from one to seven years of life is underway, taking full advantage of the prospective nature of the NINCDS Collaborative Perinatal Project.

Drs. Freeman and Holden have nearly completed a study of the prognosis of neonatal seizures, and have presented some of their findings at an international meeting.

Major Findings: Approximately one in twenty children (57/1000) followed to the age of seven years had at least one seizure. About one-tenth that number (4.8/1000) had active epilepsy by the age of seven. As studied in the NINCDS Collaborative Perinatal Project, active epilepsy in childhood is slightly more common in girls than boys, and approximately equal in rate in whites and blacks.

A major substudy on febrile seizures (Z01 NS 02234-04 DNB) is described separately. A number of reports, letters, and invited chapters reports have been published. It is proposed to followup these studies with a survey to establish current practice with regard to the management of febrile seizures by the various medical subspecialties. A consensus meeting has been held to concerning questions of longterm management of children with febrile seizures.

Data on the prevalence of specific seizure disorders in early childhood are now available. A presentation on this subject was made to an international child neurology meeting, and a manuscript is in preparation.

Approximately a quarter of children with epilepsy in early childhood have another major neurological handicap: mental retardation or cerebral palsy, or both. The other three-quarters of epileptic children did not have these additional disabilities. Analysis of the antecedents and clinical course in these two major groups is in progress.

Seizures occurring in the first month of life were associated with a relatively high rate of death or subsequent disability, including cerebral palsy. Neonatal seizures are a major marker of risk for subsequent neurologic morbidity.

Project Description: Project No. Z01 NS 02058-08 DNB

A report has been published concerning birthweight and gestational age as risk factors for seizure disorders. Low birthweight, immaturity and smallness for dates at term were not important antecedents of epilepsy in children free of cerebral palsy. Maternal, obstetrical, and early childhood characteristics which are associated with seizure disorders are now under study.

Future Course: Demographic data on convulsive disorders in Study children, and the univariate screen of antecedent maternal and pediatric characteristics are now complete. Multivariate analysis has begun. Selected topics of particular medical importance are being examined in sub-studies. A monograph on convulsive disorders in childhood will be prepared; target date is July, 1981.

Significance: The convulsive disorders are a common and socially costly medical problem. It is estimated that about 4 million Americans have some form of epilepsy. The cost of the epilepsies in direct payments and medical expenses has been calculated at more than $4 billion per year. The information generated in the NINCDS Collaborative Perinatal Project may contribute useful information in this important problem area.

Publications: Ellenberg, J.H. and Nelson, K.B.: Birthweight and gestational age in children with cerebral palsy or seizure disorders. Am. J. Dis. Ch. 133:1044-1048, 1979.

Nelson, K.B. and Ellenberg, J.H.: Seizures in early childhood (abstract). Develop. Med. Child Neurol. 22:261-262, 1980.

See Febrile Seizures.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02059-08 DNB

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Cerebral Palsy Data Analysis Group

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	K.B. Nelson	Pediatric Neurologist	DNB NINCDS
PI:	J.H. Ellenberg	Mathematical Statistician	OBFS NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Developmental Neurology Branch

SECTION
Section on Cerebral Palsy and Other Motor Disorders

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.2	0.8	0.4

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This large prospective study attempts to add to available knowledge of the perinatal factors associated with motor handicaps in childhood, the primary goal being to identify areas for possible preventive efforts.

Study on the prevalence and on early recognition of cerebral palsy have been published. Data on demographic analysis and a univariate screen of maternal and pediatric factors associated with cerebral palsy are available. Multivariate analysis is nearing completion.

Project Description: Project No. Z01 NS 02059-08 DNB

Objectives: To examine the etiology of motor disabilities in children, to improve clinical prediction, and to examine the relative frequencies of motor and associated disabilities in the population of the NINCDS Collaborative Perinatal Project.

Methodology: The univariate screen relating antecedent obstetric variables and early clinical manifestations with regard to their association with cerebral palsy diagnoses has been completed and multivariate analyses have begun. The analysis of demographic factors (e.g., institution, race, socioeconomic status, etc.) and their impact on the incidence and risk of cerebral palsy is available. Study of the natural history of cerebral palsy from one to seven years of life has been performed, taking full advantage of the prospective nature of the NINCDS Collaborative Perinatal Project.

Future Course: The multivariate analysis of the obstetric, early clinical and demographic factors is under way.

Major Findings: Cerebral palsy at seven years is somewhat more frequent in boys than girls, and among whites than blacks. Twelve per cent of cerebral palsy is apparently caused by events occurring after the first month of life, most often infection or trauma.

Clearly handicapping cerebral palsy was present at age seven in 22-33/10,000 children, the range being related to race and sex. Within each birthweight and gestational age group examined, white males were at highest risk of cerebral palsy.

A listing of maternal and pediatric conditions most strongly associated with cerebral palsy outcomes has been made, and is the basis for multivariate analysis.

Studies have been completed concerning:

1. The relationship of birthweight and gestational age to cerebral palsy (CP). Although low birthweight and immaturity are risk factors for CP, 59% of CP and 69% of CP other than spastic diplegia, occurred in infants of term weight and full 37 or more weeks gestational age. Preterm infants with later CP tended to be undergrown even considering their short gestations.

2. Signs of neonatal neurologic dysfunction as predictors of CP. Certain signs on neonatal neurological examinations, and observations in the newborn nursery, are strongly associated with the likelihood of later CP. This study permits evaluation of the potential utility of neonatal mass screening programs for motor deficits.

3. Apgar scores as predictors of longterm neurologic morbidity. Very low Apgar scores at ten, 15 and 20 minutes identify surviving babies at high risk for CP, which in this circumstance is usually accompanied by severe mental retardation and often by seizure disorders.

Studies are now in manuscript form concerning:

1. Early recognition of the infant at high risk for CP. Findings on examination at four months of age have been evaluated for utility in the early recognition of infants at risk for motor handicap. An infant who was considered to be neurologically abnormal at age four months, was at 100 times the risk of CP at age seven years as a baby who was considered neurologically normal when four months old.

2. Associated handicap in children with CP. In addition to motor disability, children with CP have an increased frequency of intellectual, sensory and behavioral disorders, and seizure disorders. This study quantifies the degree of the association of CP with other handicaps, according to severity of CP and to specific CP type.

3. Children who "outgrew" CP. Subjects who were free of CP at seven years were more likely to be mentally retarded, to have recurrent convulsions, speech articulation problems, and other disabilities if they had shown abnormal motor signs on examination at one year of age. Children with documented early motor abnormalities, especially those of mild degree, may be free of motor handicaps by early school age but at risk for other disabilities.

Significance: Approximately 750,000 persons in the United States are victims of cerebral palsy; milder forms of cerebral palsy are more frequent still. The loss in social and economic terms is immense, and individuals with CP are often lifelong dependents of their families or the state. Our aims are to identify areas in which preventive efforts may be effectively directed, to improve clinical prognostication, to examine clustering of handicaps, and to estimate relative frequency of cerebral palsy conditions.

Publications: Nelson, K.B. and Broman, S.H.: Perinatal risk factors in children with serious motor and mental handicaps. Annals Neurol.2:371-377, 1977.

Ellenberg, J.H. and Nelson, K.B.: Birthweight and gestational age in children with cerebral palsy or seizure disorders. Am. J. Dis. Child., 133:1044-1048, 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02060-08 DNB

PERIOD COVERED
October 1, 1979 through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Birthweight-Gestational Age

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: J. S. Drage	Chief	DNB, NINCDS

COOPERATING UNITS (if any)
J. B. Hardy, The Johns Hopkins University
E. D. Mellits, The Johns Hopkins University

LAB/BRANCH
Developmental Neurology Branch

SECTION
Collaborative Perinatal Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.50	0.25	0.25

CHECK APPROPRIATE BOX(ES)
☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The final analyses, including a re-run of parts of Phase II and all of Phase III have been completed. Phase II, a multivariate analysis to determine relationships with birthweight, included analyses of primigravida only, as well as all gravida. Analyses were run utilizing information prior to delivery and separately at delivery (for example, placenta weight). Phase III examines events subsequent to birth as a function of information available at birth. These results are summarized in the form of Empirical Risk Tables which describe the empirical probability of the negative outcomes within the first year of life as a function of birthweight, gestation age, race, sex and placenta weight. The structure of the manuscript has been formed into four sections: 1. Description, 2. Concomitant Events, 3. Antecedents, 4. Subsequent Risk. Emphasis for the text material over the past year has been on finalizing figures and tables Virtually all are completed. The writing of the monograph is in progress.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02062 - 08 DNB

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Minimal Brain Dysfunction

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P. L. Nichols	Research Psychologist	DNB NINCDS
Other:	Ta-Chuan Chen	Sr. Math. Statistician	OBE NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Developmental Neurology Branch

SECTION

Mental Retardation and Learning Disorders Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.90	.70	.20

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Antecedents of minimal brain dysfunction were investigated by examining the association of three major symptoms--school achievement, or learning difficulties; hyperkinetic-impulsive behavior; and minor neurological problems, or neurological soft signs -- with socioeconomic, perinatal, developmental, and familial variables. A major report describing the project is in press. Variables significantly associated with low achievement included socioeconomic status, number of family moves, family size, affected siblings, and behavior and motor performance at age 4. Hyperactivity was associated with cigarette smoking during pregnancy, size at birth and in infancy and childhood, father absent from the home, affected siblings, and behavior and motor performance at age 4. Associations with neurological signs included motor performance in infancy and at 4 years of age, cigarette smoking during pregnancy, size at birth and later, affected siblings, and neonatal seizures.

PHS-6040
(Rev. 10-76)

Project Description:

Antecedents of minimal brain dysfunction (MBD) were investigated in the population of the Collaborative Perinatal Project (NCPP). The purpose of the study was to identify children with learning difficulties (LD), hyperkinetic-impulsive behavior (HI), and neurological "soft signs" (NS) - three symptoms said to be characteristics of MBD - in this large unselected population, to examine associations among the symptoms, and to identify socioeconomic, prenatal, genetic, and early developmental factors associated with increased frequencies of the symptoms. Affected children were identified by their assigned scores on factor analytically derived dimensions representing LD, HI, and NS. The association among the three symptom areas was slight, a finding consistent with the current thinking in this area; viz., that MBD is a poorly defined category and that it is more useful to keep the areas separate than to hypothesize an underlying syndrome.

More than 300 antecedent variables were screened for associations with the three factor scores. The results replicated many findings from smaller-scale studies of clinically diagnosed children, and several previously unreported associations were found. Learning difficulties were related to low socioeconomic status and tended to run in families; the familial association was likely determined environmentally. Preschool predictors were more strongly related to hyperkinetic-impulsive behavior than were early antecedents. However, genetics, demographic factors (including father absence and only child), pregnancy complications (including maternal smoking during pregnancy), and infant development were also implicated. Like HI, neurological "soft signs" were more highly related to preschool performance than to perinatal complications and had a tendency to run in families. A book length report describing the entire project is in press.

Publications:

Nichols, P.L, and Chen, T.C.: Minimal Brain Dysfunction: A Prospective Study. Hillsdale, N.J.: Lawrence Erlbaum Associates, in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02106 - 07 DNB

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Developmental Factors Associated with Mental Retardation

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S. H. Broman	Acting Chief, MRLDS	DNB NINCDS
Other:	P. L. Nichols	Research Psychologist	DNB NINCDS
	J. P. Pomeroy	Systems Analyst	DNB NINCDS

COOPERATING UNITS (if any)

Dr. Peter Shaughnessy, University of Colorado Medical Center
Dr. Wallace Kennedy, Florida State University

LAB/BRANCH

Developmental Neurology Branch

SECTION

Mental Retardation and Learning Disorders Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.7	.5	.2

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to identify predictors of mental retardation in a population of 37,000 children followed from the prenatal period to age 7. The incidence of mild retardation (1% in whites and 5% in blacks) and to a lesser degree, of severe retardation (0.5%) was inversely related to socioeconomic status. Among the severely retarded, 25% of whites and 50% of blacks had no major genetic or neurological abnormality. Perinatal risk factors for the severely retarded group as a whole include Down's syndrome, major CNS malformations, neonatal seizures and clinical signs of perinatal hypoxia. For the subgroup of severely retarded with unknown etiology, perinatal risk factors include non-CNS malformations, peripheral nerve abnormalities, signs of hypoxia, and maternal urinary tract infection during pregnancy. A report on teenage pregnancy as a risk factor for poor cognitive outcome has been published. This study is completed and a monograph is in preparation.

[illegible]-6040
(Rev. 10-[illegible])

Publications: Broman, S.H.: Longterm Development of Children Born to Teenagers. In Scott, K., Field, T., and Robertson, E. (Eds.): *Teenage Parents and Their Offspring*. New York; Grune and Stratton, 1980.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02107-07 DNB

PERIOD COVERED
October 1, 1979 through September 30, 1980

TITLE OF PROJECT (80 characters or less)
The Study of Visual Abnormalities in the NINCDS Collaborative Perinatal Project

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: R. Feinberg	Research Psychologist	DNB, NINCDS

COOPERATING UNITS (if any) W.R. Baldwin, New England College of Optometry; R.E. Hoover, Baltimore, Md.; R.P. Kling, Georgetown Univ. Hosp.; M.A. Whitcomb, Nat. Acad. of Sc.; S.Z. Wood, Washington, D.C.; F.A. Young, Wash. State Univ.

LAB/BRANCH
Developmental Neurology Branch

SECTION
Collaborative Perinatal Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	0.0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project includes the analysis between visual abnormalities in NCPP children and predictor variables; anecdotal treatment based on case histories of unusual visual abnormalities; special studies of high-incidence disorders; case studies of the blind children; and, preparation of a monograph encompassing these subjects. Basic data analysis is complete and the manuscript of the monograph is in preparation.

PHS-6040
(Rev. 10-76)

Project Description:

The objectives of this project are to determine the extent to which genetic, maternal, obstetric, pediatric and environmental factors produce eye and visual abnormalities in the NCPP children; to assess the relative frequency of such anomalies; and, to study the concomitance of visual abnormalities with other sensory and motor neurological and systemic disorders.

Data analyses are now complete and the monograph report is in preparation. The following is an outline of the book as currently perceived.

1. Preface
2. Foreword
3. Introduction
4. The Collaborative Perinatal Study

Background of Study
Original Purpose
Expansion of Project
The Study Population, Cohort and Sample
Composition of the Study Population
Selection of the Collaborating Centers and of the Gravidas
Composition of the Study Population
Characteristics of Women Lost to the Study
Characteristics of the Mother and Family in the Study
Socioeconomic Considerations

5-A. Frequencies of Eye Conditions
B. Vision Abnormalities in Relationship to the Total Study

6-7. Associations with Pediatric-Neurological Variables

8. Vision Screening

9. Correlations of One Year and Seven Year Variables

10. Referred Cases- - -Anecdotal Reports

11. Special Studies: Prematurity; Retinal Hemorrhage

12-A. Appendices

12-A1. Glossary

12-A2. Forms Used

12-B. Index

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02108 - 07 DNB

PERIOD COVERED
October 1, 1979 to Sepember 30, 1980

TITLE OF PROJECT (80 characters or less)

Developmental Factors Associated with Learning Disorders

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S. H. Broman	Acting Chief, MRLDS	DNB NINCDS
Other:	E. C. Bien	Research Psychologist	DNB NINCDS
	J. D. Pomeroy	Systems Analyst	DNB NINCDS

COOPERATING UNITS (if any)

Dr. Peter Shaughnessy, University of Colorado Medical Center

LAB/BRANCH
Developmental Neurology Branch

SECTION
Mental Retardation and Learning Disorders Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.7	.5	.2

CHECK APPROPRIATE BOX(ES)

X (a) HUMAN SUBJECTS X (b) HUMAN TISSUES ☐ (c) NEITHER

X (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study identified early behavioral, physical and familial characteristics of children with average IQ scores and below average school achievement, approximately 3 of the NCPP population among both whites and blacks. Low achievers, followed from the prenatal period to age 7, were compared with their IQ-matched academically successful controls on prospectively ascertained indices of cognitive and physical development and family environment. Cognitive deficits and behavioral problems in the preschool period were associated with low achievement at age 7. Socioeconomic status (SES) and family structure were better predictors of low achievement than were indices of physical development or medical status. Low achievers were born into low SES, large families, and two-thirds of them were boys. As preschoolers, they had difficulties with verbal tasks and low IQ scores as compared with controls. At age 7, signs of deviant behavior, verbal and non-verbal cognitive deficits, and neurological soft signs were present. Hyperactive low achievers had an increased frequency of obstetrical complications. Sex differences were found in precursors as well as in the incidence of unexpected academic failure. This study is completed and a monograph is in preparation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02109-07 DNB

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)
Comprehensive Analysis of the NCPP Data on Congenital Malformations

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	N.C. Myrianthopoulos	Research Geneticist	DNB NINCDS
OTHER:	A.F. Naylor	Research Geneticist	DNB NINCDS
	F. Clerget	Guest Worker	DNB NINCDS

COOPERATING UNITS (if any)
C.S. Chung, Univ. of Hawaii; H. Lubs and M.L. Lubs, Univ. of Miami, Fla.; J. Frias, Univ. of Florida; M. Melnick, Univ. of Southern California, Los Angeles; P. Koslowe, Johns Hopkins Univ. Baltimore.

LAB/BRANCH
Developmental Neurology Branch

SECTION
Birth Defects and Genetic Disorders Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
6.00	5.00	1.00

CHECK APPROPRIATE BOX(ES)
☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This is a long-term project to study the epidemiologic characteristics of congenital malformations in singletons and twins; to assess and interpret the influence of maternal, socioeconomic, neonatal, medical and other environmental factors on the occurrence of congenital malformations; to determine the risk of familial occurrence and to elucidate the role of genetic factors and the mode of inheritance of certain malformations; to determine the severity and clinical significance of congenital malformations and their associations with neurological, psychological and sensory handicaps; and to assess the long-range effects of malformations on survival, growth and development.

PHS-6040
(Rev. 10-76)

Project Description:

Objectives: This is a long-term project to study the epidemiologic characteristics of congenital malformations in singletons and twins; to assess and interpret the influence of maternal, socioeconomic, neonatal, medical and other environmental factors on the occurrence of congenital malformations; to determine the risk of familial occurrence and to elucidate the role of genetic factors and the mode of inheritance of certain malformations; to determine the severity and clinical significance of congenital malformations and their associations with neurological, psychological and sensory handicaps; and to assess the long-range effects of malformations on survival, growth and development.

Methodology: A congenital malformation is defined as a gross physical or anatomical developmental anomaly which was present at birth or was detected during the first year of life. Malformations have been classified into major and minor categories on the basis of their severity, threat to life and cosmetic significance.

The analysis is divided in 11 parts, and for each appropriate epidemiologic and statistical methods are being employed. In addition, in-depth studies of specific malformations or group of malformations are performed.

Current status and major findings:

I. Epidemiology of congenital malformations in singletons.

This part has been completed. About 15 percent of single-born children had one or more malformations. Half of the malformations were major. Only about a third of malformations observed during the first year of life were diagnosed at birth. Except for three minor malformations which were more frequent among blacks, there were no significant differences in malformation incidences between blacks and whites.

A report of this part has been published.

II. Epidemiology of congenital malformations in twins.

This part has been completed. Twins have significantly more major and minor malformations than singletons but the difference is wholly contributed by monozygotic (MZ) twins. The incidence of malformations in dizygotic (DZ) twins is the same as that in singletons. Monoamniotic twins have more malformations than diamniotic twins. Concordance rates are significantly higher among MZ than among DZ twins for all malformation categories but among specific malformations only those of the musculoskeletal system show significant differences.

A report of this part has been published.

III. A study of the effects of medical, genetic and socioeconomic factors in the occurrence of congenital malformations.

This part has been completed. Multiple birth, pregnancy complications (mostly through hydramnios) and male birth were positively correlated with increased risk in major malformations, whereas maternal weight gain was negatively correlated with major malformations. Maternal diabetes during pregnancy was significantly correlated with single or multiple major malformations.

Over one-third of children of chronic alcoholic mothers show a constellation of developmental deficits and clinical symptoms known as the "fetal alcohol syndrome". An analysis of malformations in children of mothers who took dilantin during pregnancy shows that 11% of these children show a constellation of developmental deficits and clinical symptoms consistent with the "fetal hydantoin syndrome".

Reports of this part have been published.

IV. Special analysis of the effects of diabetes in the mother on the occurrence of congenital malformations in the offspring.

This part has been completed. The risk of having a malformed child in mothers with continuous diabetes is doubled compared to that of non-diabetic mothers, with regard to major malformations and increased significantly with regard to minor malformations. The effect seems to be associated with the severity of the disease and not with the intake of insulin.

A report for this part has been published.

V. A file for genetic studies of congenital malformations.

This part has been completed. A file has been designed to derive empiric risk figures of repeating a malformation when it has once appeared in a family; to identify familial aggregations of specific malformations; and to clarify the mode of inheritance in identified familial aggregations.

The basic file to be used in genetic analyses has been considerably enlarged and has been documented. This "Family Linkage File" contains a record for each NCPP child including all information on its relationships to other NCPP children. It also combines genetic information such as family linkages, twin zygosity, etc., with important maternal and outcome variables such as malformations, minimal brain dysfunction, mental retardation, speech and hearing disorders, seizures, cerebral palsy, and visual disorders.

VI. Study of associations of ABO and Rh blood types with congenital malformations.

This study has been designed to confirm earlier suggestions of association of blood groups with congenital malformations, based on small samples.

The study has been completed. Several associations have been detected, some of which are fortuitous. The most interesting finding is a strong negative association between mother's blood group O and anencephaly. Another strong and interesting association is between pyloric stenosis and Rh incompatibility in boys. The nature of these associations should be explored in in-depth studies.

A report with extensive tabulations has been produced and is now being prepared for publication.

VII. Study of the clinical significance of minor malformations.

VIII. Longitudinal study of development, morbidity and survival of children with malformations.

These two parts have been combined for purposes of analysis. The objective of Part VII is to establish which minor malformations are worthwhile detecting and why, and which ones can be ignored or considered as normal variants. Part VIII is a continuation of Part VII and deals with the effects of single and multiple malformations on growth and development.

All cases with multiple malformations have been carefully reviewed. Of 1,477 cases with multiple malformations, 531 were considered to have significant multiple malformations. The remaining 946 were found to have multiple minor anomalies or single malformations. Analysis of 531 cases showed that in 234 (44%) the condition was a localized error in morphogenesis (anomalad); in 154 (29%) a specific syndrome could be identified; and in 143 (26.9%) the pattern of malformation could not be identified.

A special file of multiple malformations incorporating these findings has been produced. An analysis has been designed, and is now in progress, to assess the minor and multiple malformation load and achieve a meaningful classification based on their effect on mortality and morbidity.

IX. Study of the effects of maternal factors in the production of congenital malformations.

This part has been completed. Families containing half siblings have been used in the analysis to determine maternal influences, genetic or environmental. Among informative malformations, clubfoot, congenital heart defects, umbilical and inguinal hernias, polydactyly, and café au lait spots occurred with significantly higher frequencies in half siblings than in the NCPP population. The recurrence risks of these malformations were the same in full and half siblings. While this approach cannot differentiate between genetic and environmental maternal factors, it provides clues for formulating and testing biological hypotheses.

A report for this part has been published.

X. Study of 7-year malformations.

This part will study the epidemiologic characteristics of congenital malformations in NCPP children surviving to age 7 years, make comparisons with the 1-year malformations, and provide a basis for studies of the effects of these malformations on neurological outcome, psychological tests performance, and speech, language and hearing performance.

The study is now in progress. The 7-year malformations have been defined, identified, and classified into major and minor. New codes have been assigned for comparison with the 1-year malformations and a new file containing the 1-year and 7-year malformations has been created. Frequency distributions of the 7-year malformations have been produced by race, sex and institution.

Of the original cohort of 53,257 children, 39,640 were examined at 7 years although information about malformations after 1 year is available for 47,115 children. Only 3,844 children were completely lost to study after 1 year. The lost to study children do not have a higher frequency of malformations than the other children at 1 year.

While about 15% of children were found to have major and/or minor malformations through age 1 year, about 19% are found to have malformations through age 7 years. The increase is in eye, upper respiratory tract and mouth, and genitourinary malformations, and tumors. The upper respiratory tract and mouth malformations include a large number of tooth malformations, which constitute a new diagnostic category.

A report is now being written.

XI. Correlation of minor chromosomal variants with congenital malformations.

This part has been carried out as a contract operation with Dr. Herbert Lubs, University of Colorado, Denver, as principal investigator. The study utilizes data which have been developed by five NINCDS Collaborating Perinatal Project institutions which are currently participating in the Denver-based chromosomal study of minor variants.

About 40 "independent" significant associations were found but considering the large number of analyses performed, these are not more than would be expected by chance. The most significant associations were between strawberry/portwine hemangioma and increasing amounts of qh material; and pale Q banding heteromorphisms and skin anomalies. These results indicate that the total amount of qh or p11 and p13 material may be more important in the determination of developmental anomalies than any particular heteromorphism per se.

The study has been completed and an extensive report has been produced. This is now being prepared for publication.

In-depth studies of congenital malformations

These studies have been planned as a logical extension of the original Program Plan for Comprehensive Analysis of the NCPP Data on Congenital Malformations. The specific objective is to study the epidemiologic and genetic characteristics, and natural history of specific malformations or groups of related malformations.

1. External ear malformations.

This study has been completed. The frequency of external ear malformations was 1.72% in blacks and 0.42% in whites. The frequency of familial cases was 6% in both races. Segregation analysis showed that there was a substantial number of chance isolated cases. In hereditary cases, no distinction could be made between a common recessive trait with 40% penetrance and a rare dominant trait with 20% penetrance, or genetic heterogeneity. A most interesting finding was a significantly increased risk for hearing loss and speech abnormalities among white sporadic cases and a lesser increase among black sporadic cases.

A monograph-length report has been published.

2. Maternal exposure to radiation and childhood tumors.

The relative risk of childhood malignancies was found to be 2.61 that of controls when mothers were exposed to radiation prior to pregnancy, and 1.5 when mothers were exposed during pregnancy. The risk was approximately the same for malignant and benign tumors. High dose examinations consistently had a higher risk than medium dose examinations.

A report has been written and is now in press.

3. Hyperthermia as a possible teratogenic agent in man.

The offspring of pregnancies exposed to high fever during the first trimester did not show significant differences from controls with regard to growth deficiencies, neurologic abnormalities or dysmorphic features. Incremental increase in fever height was negatively correlated with Binet scores but other variables such as socioeconomic status and etiologic agent could not be eliminated as alternative explanations for this finding.

A report has been published.

4. Neural tube defects

This study will attempt to gain insight into the etiology of neural tube defects by comparing the distribution and behavior of a large number of pre- and perinatal factors in patients and controls. The records of 85 patients and over 400 random controls were extensively reviewed. Clinicopathologic correlations are being made which include gross and microscopic neuropathologic findings, measurement and weight of internal organs, and gross and microscopic examination of the placenta. Epidemiologic and genetic analyses are in progress.

5. Microcephaly

This study will define measurement and clinical microcephaly, and the relation between the two; and investigate those pre- and perinatal variables which may be significant in the occurrence of microcephaly. In a normal group of children correlations between head size and body length were significant, indicating that body length should be taken into account when head size is used as a variable. Norms for head size (corrected for body length) have been derived. An analysis of IQ scores showed that even in normal children head size is positively correlated with IQ. The analysis is now being extended to children with IQ below 70, and children with other neurological signs and congenital malformations to determine what combination of factors make up the syndrome of clinical microcephaly.

6. Pyloric stenosis

This study will examine possible etiologic mechanisms of pyloric stenosis by comparing the distribution and behavior of pre- and perinatal variables in patients and controls. The records of 105 patients and 210 matched controls have been extensively reviewed. Preliminary analysis continued the association of pyloric stenosis and Rh incompatibility. The NCPP sample is now being augmented by addition of cases ascertained in the Baltimore area.

The study is in progress.

7. Congenital heart defects

This study will attempt to identify genetic and enviromental factors which may be significant in the etiology of congenital heart defects by comparisons of the distribution of a large number of pre- and perinatal variables in patients and controls and by special genetic analysis. Extensive abstracting of records of 392 cases and 784 matched controls has been accomplished and a special file for analysis has been produced. The analysis has been designed and is currently under way. A special genetic segregation analysis has been completed. The results did not suggest major genes as an explanation for the clinical variation; a multifactorial hypothesis, with both genetic and environmental variables acting, seems to fit the data well.

Publications:

Melnick, M. and Myrianthopoulos, N.C.: External Ear Malformations: Epidemiology, Genetics, and Natural History. New York, Alan R. Liss, 1979.

Havlik, R.J., Garrison, R.J., Katz, S.H., Allison, R.C., Feinleib, M. and Myrianthopoulos, N.C.: Detection of genetic variance in blood pressure of seven-year-old twins. Am. J. Epidemiol. 109:512-516, 1979.

Clarren, S.K., Smith, D.W., Harvey, M.A.S., Ward, R.H. and Myrianthopoulos, N.C.: Hyperthermia--a prospective evaluation of a possible teratogenic agent in man. J. Pediatr., 95:81-83, 1979.

Clerget-Darpout, F. and Bonaiti-Pellie, C.: Epistasis: an alternative to the hypothesis of linkage disequilibrium in HLA associated diseases. Ann. Hum. Genet., in press.

Shiono, P.H., Chung, C.S. and Myrianthopoulos, N.C.: Preconception and intrauterine diagnostic medication, and childhood neoplasia. J. Natl. Cancer Inst., in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02112-07 DNB

PERIOD COVERED
October 1, 1979 through September 30, 1980

TITLE OF PROJECT (80 characters or less)

Neonatal Hyperbilirubinemia

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. S. Drage	Chief	DNB, NINCDS

COOPERATING UNITS (if any)
P. C. Scheidt, USUHS, Department of Pediatrics
J. B. Hardy, The Johns Hopkins University
E. D. Mellits, The Johns Hopkins University

LAB/BRANCH
Developmental Neurology Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.05	0.02	0.03

CHECK APPROPRIATE BOX(ES)
☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The neonatal hyperbilirubinemia study has been designed to assess the relationship of intermediate levels of serum bilirubin on the subsequent neurological and mental development of NINCDS Collaborative Perinatal Project children. There has been increasing concern that neonatal serum bilirubin levels between 10-20 mg% may be damaging to the central nervous system, not in the classical sense of 'kernicterus' associated with levels above 20 mg%, but rather damaging in more subtle yet clinically significant ways. Neonates have been studied in five birthweight-gestational age categories, by three socioeconomic classes, for a variety of outcome measures, including mental and motor assessments at age 8 months, and a spectrum of neurological findings at age one year which will include motor performance, reflexes, tone, abnormal movements, eye findings and the overall neurological classification of normal, suspect or abnormal. The analysis of Phase I of this study has been published. The analysis of Phases II and III, which include data obtained at ages four and seven years, has been nearly completed. Final tabulations and a report for publication are expected this year.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 NS 02169 - 06 DNB

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)
Obstetrical Medication and Development in Infancy and Early Childhood

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S. H. Broman	Acting Chief, MRLDS	DNB NINCDS

COOPERATING UNITS (if any)
Dr. Yvonne Brackbill, University of Florida
Dr. Peter Shaughnessy, University of Colorado Medical Center

LAB/BRANCH
Developmental Neurology Branch

SECTION
Mental Retardation and Learning Disorders Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.08	.06	.02

CHECK APPROPRIATE BOX(ES)

X (a) HUMAN SUBJECTS   X (b) HUMAN TISSUES   ☐ (c) NEITHER

X (a1) MINORS   (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study investigated relationships between obstetric medication and physical and cognitive development through age seven. Subjects were full term infants born to mothers with uncomplicated pregnancies and deliveries. The cohort was drawn from two hospitals in the NCPP. Pharmacological agents evaluated were inhalation anesthetics and six other drugs administered during labor and delivery. Outcomes in the first year of life included items from pediatric and psychomotor assessments. Later outcomes were scores from psychometric examinations, and items from a pediatric neurological examination. Univariate associations between outcomes and drugs were identified, and the significant relationships were examined in multiple logistic regression analyses with other relevant risk factors included. The results suggest that inhalants are associated with deficits in early psychomotor and neuromotor functioning, and that oxytocin is also associated with psychomotor deficit. Scopolamine and secobarbital are related to respiratory difficulties in the newborn, and inhalants, scopolamine, and secobarbital are associated with palpable liver at 4 months. At older ages, scopolamine is associated with slightly lower scores on some cognitive tasks, and oxytocin is associated with lower achievement test scores. A report is in preparation.

PHS-6040
(Rev. 10-76)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02171-06 DNB

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Compendium of Heritable Disorders of the Nervous System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	N.C. Myrianthopoulos	Research Geneticist	DNB NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Developmental Neurology Branch

SECTION
Birth Defects and Genetic Disorders Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.10	0.05	0.05

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose is to prepare a comprehensive list of all known heritable disorders of the nervous system, including disorders and malformation syndromes which, though not primarily neurological, have neurological involvement.

PHS-6040
(Rev. 10-76)

Project Description:

Objectives: To prepare a comprehensive list of all known heritable disorders of the nervous system, including disorders and malformation syndromes which, though not primarily neurological, have neurological involvement.

Methods employed: Sources for the compendium are published reports in the past and current literature containing convincing evidence of familial occurrence.

Current status: Recent additions to and deletion from the list have brought the number of neurological disorders to over 900. These have been classified into 23 nosological categories, including malformations, spinal atrophies, ataxias, demyelinating disorders, epilepsies, metabolic disorders, neuromuscular disorders, neoplasms and vascular disorders, mental retardation, syndromes, and others. The list is constantly being revised as new information becomes available.

Publications: None

SMITHSON'AN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 NS 02234-05 DNB

PERIOD COVERED
October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Febrile seizures study

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	K.B. Nelson	Pediatric Neurologist	DNB NINCDS
PI:	J.H. Ellenberg	Mathematical Statistician	OBFS NINCDS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Developmental Neurology Branch

SECTION
Section on Cerebral Palsy and Other Motor Disorders

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.6	PROFESSIONAL: 0.4	OTHER: 0.2

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The NINCDS Collaborative Perinatal Project has provided a large prospectively defined pediatric population, unselected for level of risk, in which to investigate the prevalence and natural history of the most common convulsive disorder of childhood, febrile seizures.

A series of papers has delineated the natural history of febrile seizures, and has identified risk factors for unfavorable outcome, and has reviewed the effect of sample selection on outcome. An NIH Consensus development meeting on Long-term Management of Children with Febrile Seizures was held. Results of the consensus meeting, held in this year, are being prepared for publication in professional journals, and the papers are being edited for a monograph. A pilot study of cognitive and behavioral effects of anticonvulsant medication in children with febrile seizures is underway, and a major study planned which will evaluate the effects of medications and of recurrent seizures. A program announcement is planned to invite experiments on the effects of anticonvulsant agents on the developing nervous system.

Project Description: Children in the population of the NINCDS Collaborative Project who experienced febrile seizures were identified, and their seizure histories and subsequent histories examined.

Objectives: To evaluate the prevalence, associated conditions, and prognosis of this extremely common convulsive disorder. Quantification of the risks associated with febrile seizures is necessary for rational decision-making as to therapy.

Methodology: Information abstracted from the records of children with febrile seizures was used to create a tape for data analysis on a time-share system in the Office of Biometry and Epidemiology. Clinical characteristics of children with febrile seizures, and other seizure experience by the age of seven years, as well as results of intelligence testing at seven years, were examined. Sibling controls of children with febrile seizures were evaluated.

Results: Of 1821 children with febrile seizures in the Collaborative Project population, 1706 were followed to the age of seven years. Two per cent had become epileptic by the age of seven, and another one per cent had had at least one afebrile seizure not meeting the definition of epilepsy employed. Race, sex, birthweight and Apgar score were not significant predictors of epilepsy, but clinical features of the seizures, abnormal neurological status prior to the first seizure, and afebrile seizure disorders in the immediate family increase the risk of epilepsy in a child who has had a febrile seizure.

Comparison of 431 children who have had febrile seizures only with their seizure-free siblings indicates that febrile seizures do not "cost" the child a loss in IQ, or an increased vulnerability to early learning disorder. There were no deaths and no acquired motor defects associated with febrile seizures in this series.

Predictors of recurrence, and further refinement of the relationships of characteristics of the child and types of febrile seizures to the risk of subsequent convulsive disorders have been presented. Current activities on this topic include a proposed survey. A consensus meeting on the management of children with febrile seizures was held and an edited monograph on this topic is in preparation. A pilot study of cognitive and behavioral effects of anticonvulsant medication in children with febrile seizures is underway, and a major study planned which will evaluate the effects of medications and of recurrent seizures. A program announcement is planned to invite experiments on the effects of anticonvulsant agents on the developing nervous system.

Significance: Three to four percent of children experience at least one febrile seizure. This is the most common seizure disorder in any age group, and one of the most common acute problems in child neurology. Considerable disagreement as to optimal medical management exists, and it has been our objective to supply clinically useful information as to the spectrum of risks associated with febrile seizures, as a component in therapeutic decision making.

Honors and Awards: Public Health Service Special Recognition Award to Dr. Nelson, 1977

Public Health Service Special Recognition Award to Dr. Ellenberg, 1978

Publications:

Nelson, K.B.: Febrile Seizures. In Swaiman, K. and Wright, F. (Eds.): The Practice of Pediatric Neurology. St. Louis, C.V. Mosby Co., 2nd edition, 1980, in press.

Nelson, K.B.: Febrile seizures. In Moss (Ed.): Pediatrics Update: Reviews for physicians. New York City, Elsevier, 1980.

Nelson, K.B. and Ellenberg, J.H.: Letters on febrile seizures. Pediatrics 65:677-680, 1980.

Ellenberg, J.H. and Nelson, K.B.: Sample selection and the natural history of disease: studies of febrile seizures. JAMA 243:1337-1340, 1980.

Nelson, K.B. and Ellenberg, J.H.: Long-term psychological outlook for children whose first fit occurs with fever (letter). Develop. Med. Child Neurol. 21:396, 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02332-03 DNB

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Analysis of NCPP Twin Data

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	N.C. Myrianthopoulos	Research Geneticist	DNB NINCDS
Other:	F. Clerget	Guest Worker	DNB NINCDS

COOPERATING UNITS (if any)

NHLBI; M. Melnick, University of Southern California, Los Angeles

LAB/BRANCH

Developmental Neurology Branch

SECTION

Birth Defects and Genetic Disorders Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.00	0.80	0.20

CHECK APPROPRIATE BOX(ES)

x (a) HUMAN SUBJECTS   x (b) HUMAN TISSUES   _ (c) NEITHER

x (a1) MINORS   _ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This is a secondary area within the program plan for analysis of NCPP data. The objectives of the project are to assess and interpret the influence of maternal, socioeconomic, neonatal, medical and other environmental factors on survival, growth and development, and on abnormal outcome of twins.

PHS-6040
(Rev. 10-76)

Project Description:

Objectives: The objective of the project is to assess and interpret the influence of maternal, socioeconomic, neonatal, medical and other environmental factors on survival, growth and development, and on abnormal outcome of twins.

Methodology: Twins have been classified into monozygotic (MZ) and dizygotic (DZ); and MZ twins into monochorionic (MC) and dichorionic (DC). Comparisons between and among these groups, including singletons, will be made using concordance, correlation and heritability statistics.

Current status and major findings: Studies of the effects of chorion type on normal and abnormal variation showed that chorion type has no effect on and cannot explain the higher frequency of congenital malformations in MZ twins. Likewise, chorion type has no effect on head circumference, height, and right-left asymmetry of dermal ridges. Dichorionic MZ twins have a significantly greater within-pair variation than monochorionic MZ twins for these variables. These data offer little support to prior speculations that monochorial placentas may provide less favorable environment for fetal development.

Currently, the hypothesis is being tested that the higher frequency of congenital malformations in MZ twins than in DZ twins and singletons is due to a 2-hit process which disrupts the developmental genetic clock of the embryo and renders it susceptible to the action of subtle environmental agents. The frequencies of several such variables as drug intake, viral infections, febrile episodes, etc. during pregnancy of mothers of MZ twins are being compared to that of mothers of DZ twins and singletons, for agreement with predictions under the hypothesis.

Publications:

Melnick, M. and Myrianthopoulos, N.C.: The effects of chorion type on normal and abnormal developmental variation in monozygous twins. Am. J. Med. Genet. 4:147-156, 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 NS 02390-02 DNB

PERIOD COVERED

October 1, 1979 to September 30, 1980

TITLE OF PROJECT (80 characters or less)

Huntington's chorea twin study

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	N.C. Myrianthopoulos	Research Geneticist	DNB, NINCDS
OTHER:	A. Williams	Visiting Associate	ET, NINCDS

COOPERATING UNITS (if any)

ET, NINCDS; E. Roberts, City of Hope Medical Center, Duarte, Calif.; A. Butterfield, Univ. of Kentucky, Lexington

LAB/BRANCH

Developmental Neurology Branch

SECTION

Birth Defects and Genetic Disorders Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.25	PROFESSIONAL: 0.15	OTHER: 0.10

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Using the twin method, this study will investigate genetic and environmental factors which may be responsible for the considerable epidemiologic and clinical variability in Huntington's chorea, and determine the nature of gene-environment interaction in this disease.

Project Description:

Objectives: The objectives of this study are to investigate and identify those genetic and environmental factors which may be responsible for the considerable variability in age of onset, behavioral manifestations, clinical features, and biochemical findings of Huntington's chorea, and to determine the nature of gene-environmental interaction in this disease.

Methodology: The cooperation of monozygotic (MZ) and dizygotic (DZ) twins, one or both of whom are affected, will be secured through voluntary agencies. The twins will be admitted to the Clinical Center of the NIH for observation and study. MZ and DZ twins will be compared with regard to a number of epidemiologic, clinical and biochemical variables, including family history, age of onset, clinical findings, neurotransmitter levels, fibroblast growth rate, and red cell spin resonance.

Current status: Active participation in this study has proven difficult and has been discontinued. The study is now conducted entirely by NINCDS clinical staff.

Publications: None

ANNUAL REPORT
October 1, 1979 -- September 30, 1980

Stroke and Trauma Program

National Institute of Neurological and Communicative Disorders and Stroke

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N01-NS-8-2385 University of Rochester
N01-NS-8-2386 North Carolina Heart Association
N01-NS-8-2387 University of Oregon Health Science Center

Comprehensive Central Nervous System Trauma Centers - - - - - - - - - 23-24
N01-NS-9-2312 University of California, San Diego
N01-NS-9-2313 Albert Einstein College of Medicine
N01-NS-9-2314 University of Texas Medical Branch

ANNUAL REPORT
October 1, 1979 -- September 30, 1980

Stroke and Trauma Program
National Institute of Neurological and Communicative Disorders and Stroke

INTRODUCTION

The Stroke and Trauma Program of the NINCDS is responsible for research, related training and technical consensus activities, relevant to cerebral vascular disorders, the effects of stroke, head and spinal cord injury, neural plasticity and regeneration, CNS neoplasms, chronic pain and other related research. It also serves as the institutional focal point for research on positron emission tomography (PET), psychosurgery and manipulative therapy. Fiscal year 1980 was a year of transition in which STP consolidated its Comprehensive Stroke Center Program, brought up to speed the Comprehensive CNS Trauma Center Program, completed the initial new thrust into positron emission tomography, and funded its first program project for pain.

The Stroke and Trauma Program covers those areas and disease entities which are of the highest incidence and prevalence, cause the severest morbidity and mortality, and take the largest toll of life and suffering. Included are the vast number of head injuries, spinal cord injuries and peripheral nerve injuries, the large number of strokes and their sequelae which are becoming more apparent in an aging population, the problems of preservation and regeneration of neuronal function from these diseases, brain tumor which is the second leading cause of pediatric deaths, and chronic pain resulting in distress and loss of productivity. High priority is therefore given to applied and clinical investigations with direct relevance to the pathogenesis, prevention, diagnosis and the treatment of these diseases. The Program contains discrete as well as overlapping components of basic, applied and clinical research and utilizes the several administrative instruments of program support (research project grants, program project grants, clinical research center grants, cooperative clincial trials, resource contracts, and service contracts). The number of applications for research of program projects has been approximately equivalent to those received in FY 1979. The allocation of funding was therefore:

Stroke	35%
Trauma	27%
Regeneration	17%
Neoplasms	03%
PET	17%
Other	01%

Of the 219 grant applications received during FY 1979, 58% were approved by Study Section. Of those, some 71% were approved by Council and awarded. Therefore, of all grant applications received by STP during this year, 42% were approved and awarded.

The Cerebrovascular Clinical Research Centers (CCRC) funded to university and medical centers throughout the country make up a major segment of the stroke program. Currently there are 12 of these centers which are focal points in research on the etiology, natural history, diagnosis, treatment and the pathophysiology of cerebral vascular disease. The research programs are broad, multidisciplinary and only interrelated in a general sense. Studies carried out by the Cerebrovascular Clinical Research Centers include determining factors contributing to irreversible brain damage caused by ischemia and hypoxia in experimental models of stroke and shock. Other studies assess a variety of investigational tools, such as regional blood flow, regional glucose metabolism, mitochondrial function, ion flux, tissue metabolites, cortical redox states and ultrastrucural examination. Clinical studies are aimed at intensive care and monitoring of stroke patients, assessment of regional cerebral blood flow measurements and improvement of medical, surgical and stroke therapy. Although the CCRC Program has been in effect for more than a decade, there have only been informal coordination and cooperation among the various centers. In the future it is hoped that by using the Stroke Center Clinical Research Program as a model method of focused clinical research and the potential of cooperative agreements, improvement in the coordination and cooperation between the CCRC program members can be obtained.

The Comprehensive Stroke Center Program is now moving into its third phase. The first phase, consisting of pilot and feasibility studies of one year duration, indicated that more complex studies on stroke patients could indeed be carried out with appropriate data generated. The second phase, currently completing its second year, has involved the development of base-line patient data information which attempts to demonstrate that the transfer of currently employed therapeutic modalities into the community does in fact have an effect on outcome, morbidity and mortality of the stroke patient. The third phase, expected to be implemented during FY 81, will focus on clinical research and outcome.

The Head Injury Clinical Research Centers, funded by grants through NINCDS, remain at the forefront of brain injury research. These institutions are involved in broad epidemiologic and therapeutic studies (partly in conjunction with the Coma Data Bank of the Office of Biometry and Field Studies, NINCDS); community organization, education, and outreach programs; and basic and clinical studies into the pathophysiology and treatment of trauma patients. The coordination and cooperation among the trauma center participants have been excellent.

Spinal Cord Injury Research contains two main thrusts; 1) to explain the secondary reaction of the spinal cord to injury and 2) to assess the effectiveness of currently available methods of diagnosis aand treatment. To that end the significant portion of spinal cord injury research is being carried out at the five Spinal Cord Injury Clinical Research Centers that are being coordinated through the efforts of the Yale Spinal Cord Injury Clinical Research Center. Considerable emphasis is being placed on the development and fostering of basic research into nervous system regeneration which is so vital for improvement in the treatment of injury to nervous tissue of all kinds.

Regeneration of the damaged central and peripheral nervous system is an area of high importance to STP. Although such an effort remains in the basic science sphere, base-line information on clinical events and appropriate stratification factors can be developed through such efforts as the Yale Spinal Cord Injury Clinical Research Center. In addition, the program is developing information on DMSO and plans further investigation into this and other modalities of treatment.

Positron Emission Tomography (PET) represents a major new thrust under the coordinated effort of STP and consumed over 17% of its budget. Some seven centers with three additional participants are actively developing their physical equipment, methodology and approach in this important new field. Considering the importance of this research tool, an effort will be made to coordinate these activites through joint meetings with the principal investigators which will be designed to insure that all programmatically important areas have been covered.

Shortages of skilled clinical investigators in each of the areas of program responsibility have given emphasis to the recruitment and development of additional investigators by utilization of institutional fellowship and teacher-investigator award mechanisms. The continuation of such efforts is of high program priority.

Thus with the funds and other resources made available to it, the NINCDS Stroke and Trauma Program has served as the institutional focal point for the planning and operation of the several research and related activities in its assigned area of responsibility. Because of limited resources both now and in the future, a reevaluation of program goals and objectives will be a continuing process. However, it is the Program intent to obtain the best possible research in all areas of responsibility so as to improve the quality of care of patients with these diseases.

I. CEREBROVASCULAR DISEASE

Cerebrovascular clinical research centers located in large university medical centers across the country now make up the largest segment of the stroke program. They are all multidisciplinary and broad in focus, with each center having interrelated clinical and basic research programs.

Investigations in these centers include the physical dynamics of blood flow, cerebral metabolism, and neurogenic control of cerebral circulation. Most centers also give strong emphasis to research on the care of stroke patients, including improved diagnosis and treatment.

In addition to the major efforts of the clinical research centers, smaller individual research projects are being conducted. These investigations range from basic laboratory studies in neurophysiology and biochemistry to clinical investigations of drug effectiveness, improvement of diagnostic devices and techniques, and development of improved surgical and medical treatment.

There are also three Comprehensive Stroke Centers in this program which are funded by contract. These centers were established to conduct community research and applied clinical research with the aim of improving the quality and the availability of services for the stroke patient.

Seven of the 12 Cerebrovascular Research Centers have been renewed during the past year. Two of these Centers, Duke University and the University of Maryland, have new Principal Investigators.

At Duke University there has been a change in the direction of the research. Emphasis is being placed on studies which will provide an understanding of recovery of function after stroke. Studies of neuronal plasticity after brain and spinal cord damage will complement studies of neurotransmitter function and studies of clinical and experimental aspects of ischemia. It is expected that this Center will assume a central role in coordinating and providing a forum for all stroke research activities at Duke.

A new Center at the University of Maryland has evolved from one which has been active for 12 years. A major core of the original research team is participating in the new center and projects are logical extensions of previous work.

These projects include studies on: pulse arrival time in stroke prognosis; computer assisted medical decision making; intracranial pressure in hemorrhagic stroke; pubertal influences on lipid metabolism in endothelial cells; cerebrovascular innervation and cerebral perivascular spaces; cerebral vascular injury in experimental hypertension; thrombogenic potential of sub-critical arterial stenoses; pulsatile vs. non-pulsatile flow characteristics.

The following are some examples of projects reported during the past year:

A. Clinical Studies

1. A total of 34 patients undergoing Superficial temporal artery - Middle cerebral artery (STA-MCA) anastomosis have been

evaluated pre- and postoperatively with measurements of regional cerebral blood flow, neurological and neurophychological evaluations and angiography. The majority of patients showed an increase in cerebral blood flow postoperatively in both the ipsilateral and contralateral hemispheres. The changes were more dramatic in those patients who had suffered completed strokes as opposed to those with only TIA's. Neurological and neuropsychological functions also improved postoperatively in the group with completed strokes. There was a definite positive relationship between the status of the preoperative collateral circulatory pathways to the brain and the function of the anastomosis. In these patients who had good collateral flow there was generally less adequate function of the anastomosis, while those patients with deficient collateral flow generally had good function of the anastomosis.

Fifteen patients who have undergone carotid endarterectomy have been studied pre-and postoperatively with the same battery of tests as described above. Unlike the anastomosis study the results are much more variable with only certain patients showing a clear improvement in cerebral blood flow. The hemodynamic effects of endarterectomy are more unpredictable than those following bypass surgery due to variations in the extent of arterial stenosis and in the adequacy of collateral circulation.

2. The problem of evaluating patient status with respect to recent history or determining efficacy of therapy based on patient response to the therapy at the bedside is difficult. The attending physician cannot wait for off-line data analysis and return - he needs the results at the bedside, available immediately, and with the most recent data included. To meet this need a microprocessor-based intracranial pressure (ICP) monitoring device has been developed. The device continuously monitors, records, evaluates, and displays ICP.

   ICP measurements are updated at 6- or 12-second intervals. A visual display of raw ICP data over the past 2 or 4 hours, depending upon the selected update rate, is produced on a TV monitor. In addition, the pressures are sorted into 5mm Hg pressure ranges and are displayed as a pressure-frequency histogram. The histogram bars represent the percentage of time that ICP was in each pressure range. This type of display provides the physician with a rapid means of determining the average ICP as well as providing information about the variability of ICP.

   The ICP data analyzer with histogram presentation and recall of data over the entire monitoring period will help the physician to evaluate therapy and make decisions based upon the individual patient response.

3. An ultrasound B-scanner has been under clinical trial for several years. High resolution and real-time capacity of the instrument coupled with the safety, speed, and reproducibility of the examination technique has made it possible to obtain good images of the carotid bifurcation in the majority of patients, some of whom

have undergone subsequent angiography for confirmation. Initial, favorable impressions prompted a prospective comparative study between carotid B-scanning and carotid angiography.

Results of these studies demonstrate that about one-third of the lesions are accurately identified in regard to extent and location as compared to the angiogram. About one-third are within one grade of that identified by angiography. Approximately one-third do not correlate well with angiography. At the present stage of developing and testing, real-time ultrasound B-scanning of the carotid arteries represents a promising adjunct to clinical practice, but so far there is no indication that it will substitute for angiography in most patients being considered for surgical treatment of ischemic cerebrovascular disease.

4. There have been very few attempts to systematically study the effects of rehabilitation treatments on the outcomes of stroke patients. One such study is now underway. The objectives of this research are:

   a) to compare the differential outcomes of conventional rehabilitation efforts with outcomes of one which includes a comprehensive program designed to remediate the perceptual deficits associated with right brain damage secondary to stroke;

   b) to describe the longitudinal impact of stroke on two differently treated groups of patients relative to a matched group of normals;

   c) to differentially describe and predict recovery of function in these two groups of patients from appraisal of data derived from demographic, clinical neurological examination, CTT scans, psychometric evaluation, and rehabilitation indicators; and

   d) to study the relationships among the above mentioned data sets in order to develop typologies which can describe the types of changes expected in subgroups of patients.

5. The overall case entry in the Cooperative Study of Extracranial/Intracranial Arterial Anastomosis has reached satisfactory monthly levels and as of this time about 750 cases have been entered. The patency rate continues to be higher than originally projected with a greater than 90% patency rate being achieved as shown in the postoperative angiograms. Currently, 73 centers on three continents are participating in the study. Every effort has been made to ensure the high quality of participating centers both at the time of entry and during the study. The goal of 1000 cases is now in sight if recent case entry continues. An interesting observation, variation in the distribution of atheromatous lesions within the extracranial-intracranial vasculature, has been observed between Japanese patients and those entered from North America and European centers.

   Since the last progress report, workshop meetings for each of the three major geographical regions have been held as follows:

(i) North American Workshop - September 11, 1979 - (London, Canada)
(ii) European Workshop - November 17, 1979 - (Florence, Italy)
(iii) Japanese Workshop - March 29, 1980 - (Kyoto, Japan)

B. Studies of Pathogenesis of Cerebrovascular Disease in Animal Models

1. Studies of the brain under "normal" conditions and under conditions altered by anoxia/ischemia are extremely complex and difficult. For this reason, investigations have not, as yet, led to establishing underlying mechanism by which cells are altered irreversibly and the limits of reestablishment of normal functioning. One of the most constraining aspects of brain investigations is the fact that function is maintained only when the cellular and subcellular components retain their structural relationships which are, however, disrupted in the course of the customary procedures for freezing and/or separation which are required for biochemical analysis. Unique optical techniques are being used to provide direct measurement of biochemical reactions associated with energy use and energy conservation in intact, functioning brain tissues of animal models. Thus, it will be possible to follow in "real-time" the processes of cellular respiration as they unfold. When results from these techniques are correlated with concomitant recordings of electrophysiological activities, it will be possible to consider the nature, time course and extent of ischemic injury. These studies will provide, therefore, a better understanding of the processes underlying anoxia and ischemia, an understanding which could be the basis of a more rational approach to clinical therapy.

2. The biochemical mechanisms underlying the reaction of neurons to injury were analyzed to determine if the same processes govern the recovery of central neurons from axonal damage produced by cerebral ischemia following stroke as from mechanically-produced injury.

   Local lesions of the locus ceruleus were shown to reduce synthesis of dopamine-B-hydroxylase; this suggests the possible reordering of neuronal synthetic mechanisms from neurotransmission to axonal regeneration. Further studies have shown that ischemic lesions in the cerebral hemisphere induce similar changes in the ipsilateral locus ceruleus.

3. The role of lipid peroxidation in damaging membranous structures with concomitant inhibition of proper function has received increasing attention owing to its possible importance in contributing to chronic vascular disease. Recent work has yielded a plausible explanation of how peroxidation of unsaturated lipids arises naturally in respiring cells as a consequence of univalent reduction of oxygen by the the mitochondrial electron transport system, yielding superoxide radical anions. These, together with their dismutation product, hydrogen peroxide, can generate highly electrophilic hydroxyl radicals which then initiate lipid radical formation -- the initial step in the free radical chain propagation process. This framework has been used to examine the biochemical events attendant to reperfusion of ischemic brain tissue following stroke.

The data obtained imply 1) that ischemic brain injury may potentiate free radical processes, 2) that overt peroxidation of lipids occurs during postischemic perfusion and 3) that recovery of ischemic brain tissues depends fundamentally on the capability of the tissues to utilize oxygen properly.

4. There is substantial and increasing evidence that platelets play a major role in formation of arterial thrombi. Considerable attention has, therefore, been focussed on the possibility that increased platelet reactivity might be of considerable pathogenetic importance in atherosclerosis and its thrombotic complications such as myocardial infarction and stroke.

   Studies in an acute vascular injury monkey model are aimed at assessing the effects of various platelet inhibiting agents, including the physiological product of blood vessels, i.e., prostacycline (PGI_2) on the prevention of clot formation in monkeys whose iliac arteries have been injured by a balloon catheter. The effect of PGI_2 as well as prostaglandin three series (PGH_3, TXA_3, PGD) on reversal of pre-existing thrombi is being evaluated by the indium-111 platelet imaging technique.

   Other questions to be addressed in the acute vascular injury monkey model are differential sensitivity of blood vessel and platelet cyclo-oxygenase to aspirin and the role of prostaglandins in vascular tone and permeability.

C. Princeton Conference

During the past three decades the Princeton Conferences have become recognized as important biannual events in the field of cerebrovascular disease. The publications summarizing the transactions of the symposium are widely used and contain critical reviews on the "state of the art" on current stroke problems as well as new and significant research material. The monograph containing the papers and discussion of the conference have become a standard reference for clinicians and students interested in stroke.

The 12th Conference on Cerebral Vascular Disease was held at Williamsburg, Virginia, March 2-4, 1980. The following topics were presented and discussed:

1. Migraine
2. Functional Imaging of the Brain
3. Diagnostic Procedures in Cerebral Vascular Disease
4. Ultrasonic Procedures
5. Studies of Cerebral Blood Flow
6. Contributions of PET Scanning to Understanding Stroke
7. Scientific Basis of Therapy in Stroke
8. Hematologic Studies in Stroke

D. Comprehensive Stroke Centers

A major responsibility of the NINCDS Extramural Stroke Program is the evaluation of the effectiveness of established and recently developed methods of stroke diagnosis, prevention and therapy. This responsibility also extends to evaluating and improving the means by which service is provided to stroke patients on a community basis.

To that end three Comprehensive Stroke Centers were established about two years ago with funding for three years to the following institutions:

Monroe County (New York) Comprehensive Stroke Center - Efficacy of stroke care facilities and personnel in an entire large county.

North Carolina Comprehensive Stroke Center - Value of stroke care facilities and personnel in three county clusters.

Comprehensive Stroke Center of Oregon - Effort of education, epidemiology, rehabilitation and clinical research in diverse areas of the state.

During this last year the existing data instruments being used in these centers and the methods of data collection were being modified in order to achieve a more uniform approach. Thus, any conclusions reached about the effectiveness of these programs will have greater significance and intercomparability. At the same time the uniqueness of each of the centers is being preserved.

E. Positron Emission Tomography Program

Nineteen program project applications were received in response to an announcement by NINCDS of available support for clinical and basic neuroscience research utilizing positron emission tomography. These applications were reviewed by a special review committee and by Council. The Stroke and Trauma Program is the focal point for coordinating and managing this activity. Seven awards were made to the following institutions:

Johns Hopkins University
Brookhaven National Laboratories
University of Miami
Sloan-Kettering Institute
University of California, LA
University of Pennsylvania
University of Michigan

Much of the effort in the Centers during the past year has been directed toward establishing the facilities needed to carry on the research activities and synthesizing compounds labeled with positron emitting isotopes. Emphasis has been placed on performing crucial validation studies that are essential steps prior to initiating studies in humans. Following are results of projects recently reported:

Progress has been made toward synthesizing labeled compounds which bind selectively with high affinity to dopamine or opiate receptors. The thrust of this program is on mapping receptors for opiates and dopamine progressing from validation studies in man under normal and disease states. A detailed mathematical model has been formulated for analyzing the data from both the opiate and receptor studies.

The cerebral metabolic response has been studied in six normal subjects using labeled fluorodeoxyglucose. Results show an increased glucose utilization by cells in the calcarine cortex contralateral to the visual hemifield which was stimulated by a patterned light stimulus. This confirms a well-established fact derived from the human clinical, anatomical, and electrophysiological literature, and also demonstrates the efficacy and sensitivity of the FDG method in determining localization of function within the human brain.

The positron emission tomography technique is being used to study the etiology and treatment of brain failure accompanying normal aging and senile dementia. The feasibility of obtaining reliable data from normal elderly and from senile dementia patients has been clearly demonstrated.

A data analysis strategy has been devised to quantitate ^{18}F-FDG uptake in nine relevant brain regions, on each side of the brain, for up to seven brain levels. In addition, right/left ratios are computed for each region; right, left, anterior, posterior, and whole-slice averages for each level and across levels; and ratios of the various regions of the whole-slice average, and similar ratios across brain levels. An interim data analysis has been completed for four patients with Alzheimer's disease, two multi-infarct dementia patients and two normal elderly controls. Although current sample size limitations preclude statistical analyses, several preliminary generalizations may be made. The glucose uptake values for all three elderly groups (SDAT, MID and controls) tend to be considerably lower than previously found with PET and ^{18}F-FDG for young normal subjects. The elderly subjects also show much greater right/left asymmetry. There also tends to be lowered activity in the frontal area relative to whole slice or whole brain averages. It is as yet unclear as to whether these apparent changes in metabolic activity are more severe in Alzheimer's disease than in multi-infarct dementia or normal controls.

Neuroanatomical functional mapping of brain in patients with schizophrenic disorders has revealed a depression of glucose utilization in the frontal cortex and a considerable asymmetry in the tracer uptake between hemispheres.

^{18}F-fluorodeoxyglucose (^{18}FDG) and ($^{13}NH_3$) are being used as indicators of abnormalities in local cerebral glucose utilization (LCMR$_{glc}$) and relative perfusion, respectively. The ECAT positron tomograph was used to scan normal control subjects and 10 stroke patients at various times during recovery. In patients with stroke, mean CMR$_{glc}$ in the contralateral hemisphere was moderately depressed during the first week, profoundly depressed in irreversible coma, and normal after clinical recovery. Quantification was restricted by incomplete understanding of tracer behavior in diseased brain, but relative local distributions of ^{18}FDG and $^{13}NH_3$ trapping reflected qualitatively the increases and decreases, as well as coupling and uncoupling, expected in stroke for local alterations in glucose utilization and perfusion. With improved knowledge of tracer behavior in diseased brain, the method has promise for mapping response to therapeutic intervention and increasing understanding of how the human brain responds to stroke.

II. SPINAL CORD INJURY

The consequences of spinal cord injury (paraparesis or paraplegia) are exceedingly costly psychologically and financially, for the afflicted, their families and their communities. Young adults, men in particular, are most vulnerable to the paralyses that follows spinal cord injury as a result of automobile, sports, and war-related injuries.

Secondary reactions following spinal cord injuries often appear responsible for much of the ensuing morbidity (and mortality). These tissue responses include edema, ischemia and hemorrhage. Were the pathophysiology leading to these secondary effects better understood, more effective treatment of spinal cord injured patients would be possible and neurologic deficits kept to a minimum. Thus spinal cord injury research has been directed at several major questions. These include explanations for the secondary (and presumably reversible) reactions of the spinal cord to mechanical injury, the development of sensitive diagnostic procedures to assess the extent of spinal cord dysfunction (as well as retained function), and the adoption of appropriate therapeutic interventions to minimize the deleterious structural and functional sequelae of spinal cord trauma.

Since it is difficult in patients to determine the extent of permanent injury and the type and level of therapy to be employed, much laboratory research remains to be conducted on animal models. Carefully controlled clinical trials in patients also will continue to provide much needed information.

The acquisition of data is necessarily deliberate, if not slow, due to the nature of the disorder being studied. Spinal injuries differ in character, and the concentration of spinal injured patients available for epidemiologic, diagnostic and therapeutic studies at any one or even several medical institutions is not overly large. Fortunately!!

For these reasons much of the patient related research is carried out at several large multi-investigator, multi-disciplinary research centers, where the necessary medical facilities and patient cohorts are available. The "relative paucity" of like-injured patients may still require coordinated research between centers using common protocols to enable statistically significant data to be gathered. The large centers are complemented by a number of more focused programs elsewhere, with the latter capable of performing fundamental studies that may ultimately be applied in an appropriate clinical setting.

A number of investigators are involved in epidemiological studies related to spinal cord injury. These evaluations are providing much needed information regarding the who, when, where and why of spinal trauma. This is of particular significance in determining preventative measures, appropriate utilization of emergency medical services, training of health professionals, initial and follow-up therapy regimens, as well as long-term care and rehabilitation services. Studies are underway to determine the correlations between initial neurologic deficits, treatment and outcome. Still other investigators are endeavoring to understand the short and long-term social, behavioral (coping and adaptation), and vocational implications of paralysis resulting from spinal cord trauma.

Available evidence suggests a constellation of factors are responsible for the post-contusion deterioration of the spinal cord, yet the mechanism(s) remain obscure.

Changes in blood flow rate and perfusion are considered major contributing factors to the breakdown in integrity and function of the spinal cord following injury.

A number of investigators continue to seek the factors responsible for changes in blood flow. Catecholamine alterations are currently considered secondary phenomena and attention has turned to membrane perturbations and membrane related enzymes such as cytochrome oxidase, monoamine oxidase and sodium-potassium ATPase. Lactic acid accumulation has been suggested as a possible causative factor in the abolition of cerebral autoregulation of blood flow following hypoxia. However, attempts at reducing lactic acid have had no effect on post-hypoxic loss of autoregulation, and a more complex etiology is being sought. Morphological studies reveal that vessels of the cord may be disrupted at several levels, including the junctions of the endothelial cells and the basement membrane. Using fluorescein and labelled albumin, researchers have shown that large molecules do not leak out of vessels to any great extent for two to three hours following injury. Smaller molecules will pass the blood brain barrier earlier.

Somatosensory evoked potentials (SEP) and vestibulospinal evoked potentials (VEP) continue to be explored in a number of laboratories for their capacity to provide detailed information regarding the functional integrity of the spinal cord following trauma. The SEP conveys the status of the ascending dorsal column afferents and has been correlated with the morphology of the cord. It is rapidly becoming an accepted diagnostic and investigative tool. Additional studies on the VEP tend to substantiate its use in monitoring ventral spinal tract functions.

Neurophysiological studies demonstrate a transient recovery of both efferent and afferent spinal cord activity one to two hours after injury, or prior to irreversible injury at two to three hours post-injury. Evidence also suggests a different timing with respect to onset of dysfunction of grey and white matter of the spinal cord, i.e., the former being compromised immediately whereas the latter remains intact for ten to twenty seconds after injury. Correlations of blood flow and neurophysiological events reveal that a dramatic drop in blood flow occurs concomitantly with the irreversible late loss of neuronal activity. Related studies show that grey matter blood flow tends to increase for twenty to thirty minutes after injury. An observation with general significance is the presence of substantial gradients of blood flow in the normal spinal cord of experimental animals.

The decreased blood flow to the spinal cord following injury appears due to direct injury to vessels of the cord and pooling of large volumes of blood in para-spinal and extremity muscles. The work of one investigative group has implicated the sympathetic ganglia and adrenal glands in the systemic blood pressure and spinal cord blood flow changes accompanying spinal cord injury. The mechanism of the response is being explored to develop methods of spinal cord monitoring based on blood pressure changes and blood catecholamine levels. These investigators find that sympathectomy abolishes the delayed traumatic ischemia following severe spinal contusion. If confirmed, and the mechanism determined, this observation may hold promise for the development of new treatment regimens for traumatic spinal cord ischemia, using pharmacological ganglionic blockers.

Several researchers are studying myelin breakdown following injury to the spinal cord. One hypothesis is that changes that occur may be initiated by the activation of membrane associated sphingolipases. These enzymes are to be studied following injury and an effort made to relate changes in their activity with the resulting myelin degradation which follows. A microisolation procedure has been developed for myelin of the brain and spinal cord and is being used to establish normal data. An assay for a marker enzyme of myelin, 2', 3'-cyclic nucleotide-3' phosphohydrolase, is being used to assess the degree of myelin disintegration. Finally, a method of radiolabelling ceramide is being used to estimate the breakdown of sphingolipids, a quantitatively significant and stable component of myelin. The use of the above mentioned techniques may lead to a better understanding of the early events in the process of myelin breakdown following spinal cord injury.

While prevention of secondary spinal cord changes leading to paralysis and the restitution of normal or near-normal function in severely injured patients are ultimate goals, the realities of the present dictate the development and use of remedial measures to maintain the health, well being, and productivity of the spinal cord injured.

Comparisons have been made of the urodynamics of patients with suprasacral versus sacral and infrasacral spinal cord lesions. Patients with suprasacral lesions are dissimilar, with neurogenic vesical dysfunction ranging from coordinated bladder and urethral activity to totally discoordinate activity. This group responds well to intermittent catheterization. Those individuals with sacral and infrasacral lesions require pharmacological and/or surgical intervention to reduce sphincter tone when intravesicular pressure exceeds 40 cms of water on a constant basis. The strength of the urethral closing mechanism seems to be the most important parameter for determining whether upper urinary tract infection and dysfunction will occur.

Large electrical currents are detected immediately after spinal cord transection. This declines over the next several days. About half of the inward directed injury potential is attributable to sodium and possibly calcium. This probably alters the ionic constituency of the axoplasm adjacent to the lesion. The latter in turn may have profound effects on the organization, localization and function of subcellular organelles, and could help determine the extent of regeneration that will follow. Six days of low level D.C. current applied across a spinal transection facilitates the rate and form of axonal regeneration in lower vertebrates. The ability of electrical stimulation to enhance restitution of function in the injured spinal cord will undoubtedly receive further attention.

Reports that the mammalian spinal cord isolated from the higher nerve centers can generate rhythmic, alternating "walking" and even galloping in the hindlimbs have appeared sporadically since the late 1880s. Further experiments suggest that the spinal cord can even be devoid of afferent inflow and still execute a rhythmic motor program, the latter arising from intrinsic pattern generators within the cord. To some investigators this suggests that the degree of autonomy of the lumbar spinal cord may not have been utilized to its full capacity as a model for studying neural and muscular plasticity, and in its potential application in rehabilitative procedures. Several investigative groups are currently absorbed in the analysis of spinal reflex walking and the supraspinal mechanisms that elicit and modify such locomotor activities.

III. HEAD INJURY

Occupational, vehicular, sports and home accidents, as well as criminal assault are responsible for several hundred thousand head injuries in the United States annually. The injuries vary widely with respect to site, severity and sequelae. The magnitude of the impact on the community is great and the allocation of resources to meet the problem is substantial, as illustrated by the establishment of regional shock-trauma centers and associated emergency medical services. The NINCDS supports an array of research efforts probing the etiology, prevention, diagnosis, treatment and care of the head injured.

The edema, ischemia and hypoxia that follow injury to the brain may be just as devastating or more so than the original insult. Hypotheses have been proposed and laboratories are exploring the contributing factors that may be associated with brain trauma.

In the instance of irreversible ischemic injury several lines of evidence converge to suggest that the initial biochemical determinant is the peroxidation of unsaturated lipid constituents of cellular and intracellular membranes by free radicals of oxygen. However, the mechanism(s) responsible for this type of tissue injury remain unresolved. For example, investigators are exploring whether the lipid auto-oxidation may be due to loss of oxygen at the terminus of the respiratory chain (undirected electron transport free radicals) or restoration of oxygen to the ischemic brain tissue by recirculation or collateral circulation. Substantiation of the free radical theory would lead to an intensification of the search for therapeutic agents directed at the preservation of metabolic and functional integrity of injured brain tissue.

Barbiturates are reputed to suppress the sequelae of cerebral ischemia and hypoxia when given before or soon after insult. When given in appropriate amounts and at the proper time the drugs appear to afford protection from focal infarction, resuscitation from global ischemia-anoxia, and control of intracranial hypertension. The four recognized direct barbiturate effects involved in the protective mechanism include reduction of metabolism, cell membrane stabilization, free radical quenching, and anesthesia. Controlled clinical trials and laboratory studies are underway at several institutions to fully evaluate the protective effects of barbiturates.

Mechanical retraction of the brain at the time of operation is a standard neurosurgical procedure employed to obtain better operative exposure. This maneuver necessitates direct pressure on brain structures and could damage brain tissue. Using a modified brain retractor investigators have recorded direct pressure exerted on underlying brain tissue and have related the degree of pressure to the development of changes in blood brain barrier permeability, the development of edema, and the development of focal ischemic cerebral infarction. Knowing in advance of this potential risk, efforts may be made to minimize retraction. Where prevented from doing so, by constraints such as operative interval or limited access to the surgical field, appropriate prophylactic measures may be instituted.

The quality of outcome after severe closed head injury is of increasing concern to neurosurgeons as advances in management may be capable of reducing mortality and increasing the number of survivors with varying degrees of disability. In contrast to a number of earlier studies suggesting that intellectual ability after severe closed head injury eventually recovers to a normal level, new preliminary findings show that residual intellectual level, memory storage and retrieval, linguistic deficit, and personal social adjustment correspond to overall outcome. The recent study shows that all severely disabled patients, as well as some that are moderately disabled, exhibit unequivocal cognitive and emotional sequelae after long follow-up intervals. Analysis of persistent neuropsychological deficit in relation to neurological indices of acute injury severity suggest the potential prognostic significance of oculovestibular deficit. The current findings indicate that protocols used in the evaluation of treatment should include long-term assessment of neuropsychological functioning. A major challenge of rehabilitation of the severely head injured remains the remedying of neuropsychological deficits.

The Galveston Orientation and Amnesia Test (GOAT) was developed to evaluate cognition serially during the subacute stage of recovery from closed head injury. This scale measures orientation to person, place, time, and memory for events preceding and following injury. The duration of impaired GOAT scores is strongly related to the acute neurosurgical ratings of eye opening, motor responding, and verbal responding on the Glasgow Coma Scale. Duration of posttraumatic amnesia, as defined by the persistence of defective GOAT scores, is longer in patients with computed tomographic evidence of diffuse or bilateral brain injury as compared to cases with focal unilateral lesions. Serial GOAT scores are also predictive of long-term level of recovery.

The effects of elapsed time after injury on learned tasks and their reversal have been tested in animals. Using tactile-discrimination training, cerebral lesioning and varying post-lesion recovery periods, it has been shown that retention of tasks and mastery of reverse training in many instances are most severely impacted at the longer post-injury interval, illustrating that not all brain lesion effects are most severe immediately after injury. Evidence in animals indicate that the deficits resulting from ablation of sensorimotor cortex can be very complex, involving factors beyond overt sensory and motor disturbances. These findings are reminiscent of a number of observations made on patients, some described briefly above, and could conceivably suggest better therapies for patients with brain lesions.

Beyond research on overt trauma, the trauma program supports a broad range of investigation in related areas.

Induced hypotension is an important adjunct in facilitating the dissection and clipping of intracranial aneurysms. Reduction of systemic blood pressure during these operations, however, may place the patient at increased risk, since the level and duration of hypotension that can be tolerated without cerebral infarction in any individual case with subarachnoid hemorrhage are unknown. The direct cortical response, a complex electrical response evoked and recorded from the surface of the brain, has been shown to be a reliable means of evaluating the electrophysiological responsiveness of the cortex during hypotension. The suggestion has been made that decreases in the amplitude of the response are related to decreases in local cerebral blood flow. Thus monitoring of a patient's direct cortical response should permit greater individualization of therapy during intracranial surgery.

A patient with an accessible, encapsulataed brain abscess who is deteriorating neurologically, or has an enlarging abscess with significant mass effect is generally treated by early surgery. However, recent studies suggest that an initial trial with antibiotic therapy may be warranted in patients who 1) are considered poor surgical candidates, 2) have multiple abscesses, especially if distantly located from one another, 3) have abscesses in a deep or dominant location, 4) have concomitant meningitis or ependymitis, 5) have concomitant hydrocephalus requiring a cerebrospinal fluid shunt that might become infected during abscess surgery, 6) or show partial abscess resolution attributable to antibiotic therapy. Additional efforts are underway to correlate diagnostic criteria and appropriate antibiotic interventions.

Other avenues being studied for their potential insight into the pathophysiological processes associated with CNS trauma include:

-- "Osmotic Regulation, Neurotransmitter Metabolism aand Brain Edema,"
-- "Increased Intracranial Pressure and Central Neurogenic Pulmonary Edema,"
-- "Membrane Methylation in Brain Edema,"
-- "Transport Systems of the Choroid Plexus."

IV. CNS NEOPLASMS

The Stroke and Trauma Research Program into CNS Neoplasms is of modest size and contains some 14 research grants. These include basic, applied and clinical research projects.

Investigators are evaluating the correlation of circulating levels of brain antibodies and antigens utilizing immunodiagnostic tests for specific glial markers. Such proteins as S-100, myelin basic protein and other related substances are being examined.

Neuropathologic investigators are examining the frequency, distribution and functional characteristics of capillary and endothelial defects which exist within experimental gliomas. They are specifically concerned about the brain adjacent to tumor (BAT), where interface and invasion between tumor and normal brain takes place. They are developing models including the avian sarcoma virus induced glioma in order to have a reproducible and steady model on which to conduct experiments. It is hoped that this model might be translated to investigation of ocular tumors as well. Hyperthermia has been shown to enhance both the effects of ionizing radiation and chemotherapy. This extremely important area is beset with many logistic and mechanistic problems in terms of delivering focused heat to specific areas of the brain and controlling it. Researchers are utilizing focused microwave induction using multiple ports in order to carry out at first dosimetry planning and later therapeutic studies.

It is presumed the glioma cells have an aberration in their metabolic pathway which has resulted in their becoming neoplastic. The C6 astrocytoma cell line has a decrease in cAMP production after exposure to norepinephrine which may be due to induction of phosphodiesterase. Studies are being carried out to identify which proteins show neurotransmitter activity and whether cAMP dependent phosphorylation may be utilized as a method of cell regulation. Additional work is being pursued to develop specific clones of brain tumors which might be utilized for extensive comparative testing, understanding of the metabolic regulation of glioma cells, research into screening technology for the radiosensitizers, and kinetic analysis and regulation of brain tumor phosphotransferase.

The Stroke and Trauma Program has an interest and intent of increasing its activity into basic and applied research in the treatment of malignant brain tumor. It is proposed to have several meetings during the course of the year which will help to define those areas in CNS neoplasm to which more attention should be paid and to stimulate research in the treatment of this most devastating disease.

V. NEURAL REGENERATION AND PLASTICITY

The scientific communities' interest in development and regeneration of the nervous system has expanded greatly in recent years. With this heightened interest has come a growing awareness that basic hypotheses must be proposed and fundamental experiments conducted before the enigma of central nervous system regeneration is resolved. A fifth biennial Conference on Regeneration in the Central Nervous System, supported by the NINCDS, was convened in May, 1979. The title of the Conference, "Cellular Mechanisms for Recovery from Nervous System Injury," exemplifies a major trajectory being taken with respect to research on regeneration and plasticity, especially that associated with spinal cord injury.

Neural regeneration, where evident, is accomplished through either extension of neurites (the regrowth of severed axons) or collateral sprouting (the branching and growth of undamaged axons). A variety of studies have established the disparate regenerative capabilities of different components of the nervous system. Peripheral somatic nerves, for example, regenerate by extension and sprouting. However, the regeneration is rather inaccurate with respect to peripheral effectors. The peripheral autonomic nervous system exhibits regeneration and often a very selective reinnervation of effectors ensues. The central nervous system exhibits the potential for reinnervation by collateral sprouting and extension. However, in most instances the results leave much to be desired. Directly traumatized and adjacent neural tissues may suffer drastic, irreversible damage following injury, with the long tracts, in particular, exhibiting little sustained capacity for regrowth and renewal of functions.

In an effort to resolve the biological complexities associated with regeneration in the nervous system, investigators are following a number of promising avenues of research. Developmental factors, for instance, are coming under increasing scrutiny in an attempt to understand how the nervous system, at its inception, arranges its components and makes all the appropriate connections. Several cues, presumably responsible for the establishment of a purposeful neural circuitry, are receiving extensive attention. Mechanical guidance may be provided by the growth and disposition of ependymal cells, neuroblast and glial alignment, and initial axonal orientation leading to fascicle formation. Chemotaxis, or development guided by diffusible molecules, may play a role in stimulating and in determining the direction of cell migration and neurite extension. Nerve Growth Factor is one known candidate for this latter function, but others appear to be undergoing first disclosure. Haptogenesis is a mechanism whereby molecules fixed in a substrate act as guidance cues for neurons and their axons. Programmed cell death undoubtedly plays an important role in the elimination of redundant features and establishment of the final configuration of the nervous system. Trophic influences, exerted by one cell upon another, may regulate the anabolic activity of cells and determine whether a neuron barely survives, is maintained in good fashion, or is prompted to exceptional activities requiring unusual resources. Specifying agents evidently channel selective use of the trophic drive into specific efforts, e.g., growth versus production of a unique protein. The properties of membranes and the metabolism of neurons and glia are perceived as playing major roles in the maintenance and adaptability of the nervous system.

Axoplasmic transport, neurite extension and synaptogenesis are manifestations of the interaction of intra- and extraneuronal capabilities. An understanding of the internal and external microenvironnments associated with these processes will permit reasoned efforts at manipulating these milieu and thereby achievement of the most successful neural regeneration possible.

Observations of significance to neural regeneration are emanating from a number of investigators using a variety of experimental models. Included are studies on normal and nervous system-injured animals, the immature and the mature, mammalian and non-mammalian species, and in vitro as well as in vivo preparations.

Investigators at several institutions are providing additional evidence for specific substrate pathways in the developing and mature nervous system. This supposes that substrate pathways are established early during ontogeny, i.e., on the neural plate or its precursors, and furthermore, that these preferential guidance systems are retained, in varying degrees of expression, through maturity.

Despite already extensive efforts devoted to unraveling the composition and mechanism(s) of action of Nerve Growth Factor (NGF), this substance continues to undergo further characterization by several research groups and its physiological role probed by still others. Green and colleagues have employed a pheochromocytoma cell line (PC12), in vitro, as a model system for studying neuronal differentiation. In the presence of NGF the PC12 cells cease to divide, extend protoplasmic processes, become electrically excitable and exhibit increased excitability to acetylcholine. Thus this system permits the investigator to discern biochemical, structural, and functional changes that accompany cellular differentiation. Among the earliest responses of PC12 cells to NGF are alterations in the configuration of the surface membrane (possibly attributable to membrane receptor responses); increased rate of uptake of small molecules - like amino acids; and the induction of ornithine decarboxylase (which may mediate cellular responses to hormonal or replication factors), and a transcription dependent 80,000 molecular weight polypeptide. NGF also promotes the incorporation of certain carbohydrates into membrane associated components including membrane related glycoprotein. Further studies are necessary to determine how the above noted changes relate to development and regeneration of neurons in vivo.

The constituents of axoplasmic flow continue to be scrutinized by Lasek and others. Fast and slow components of streaming axoplasm have been described. The slow component of axonal transport consists of two principal subcomponents, Slow-Components a and b (SCa and SCb). SCa represents the neurofilament-microtubule network which is continually conveyed from the cell body to the axon terminal. SCb apparently represents another cytoskeletal network, which is hypothesized to be the microtrabecular system. The network formed by SCb contains actin-microfilaments, clathrin and a large number of other proteins. This network is transported within the axon at a rate three to five times faster than the neurofilament-microtubule network. Electron micrographs of the microtrabecular system indicate that it is associated with the neurofilament-microtubule network. However, even though the two networks apparently move past one another at different rates, no intermixing of the proteins of SCa and SCb has been detected. These observations demonstrate that as the understanding of the transport of the axonal cytoskeleton advances, the ability to generate testable hypotheses about axonal growth and regeneration advances in parallel.

McMahan and colleagues have demonstrated, at neuromuscular junctions, that following removal of nerve terminals and myofibers from muscles, factors remain at synaptic sites that direct the growth of axons and the formation of pre- and postsynaptic specialization in regenerating nerve and muscle. Some of the factors are associated with the synaptic basal laminar, since reinnervation preferentially occurs at the site of the original synapse. The identification of structures that provide information to regenerating synapses and the nature of the information provided are important steps toward identifying molecular elements that regulate synapse formation. The manner in which the responsible molecules are regulated is also germane to an understanding of the process by which appropriate synapses are formed. Such studies provide important information regarding development and regeneration in the peripheral nervous system and establish a simple model for determining the direction of related studies in the more complex neuropil of the central nervous system. Cotman and colleagues, working in the central nervous system, have found that virtually all glycoproteins in isolated synaptic junctions are located on the external surface of the junction, within the synaptic cleft. These investigators have undertaken the purification and characterization of these glycoproteins in the belief that they may play an important role in the initial recognition process during synaptogenesis.

Grafstein and colleagues have undertaken further analysis of the retrograde effects of a "conditioning lesion" imparted to nerve cell axons. Studies on severed goldfish optic axons reveal a doubling in the speed of axon elongation if a nerve crush precedes, by two weeks, the cutting of the optic tract. Furthermore, the delay before appearance of the regenerating axons is halved as a result of the conditioning lesion. Similar effects have been observed in the rat sciatic nerve, with the optimum interval between axonal insults being two to twenty-eight days. These results indicate the mutable nature of neuronal regeneration. Inquiry into the responsible mechanisms could lead to more specific means of manipulating the regeneration process.

Rovainen and Stelzer, in separate studies, have observed regeneration of descending giant axons in larval lamprey following spinal cord transection. They have correlated recovery of locomotor behavior with regeneration of the giant reticulospinal cells. Wood and Cohen have recently verified that the regenerating axons of Mauthner and Muller Cells may extend several millimeters beyond the level of cord transection and that coordinated swimming activity returns to the lampreys several months after the spinal cord injury. The latter investigators, using an intracellular marker and electron microscopy, have described the considerable branching of regenerated axons following cord transection, as well as the presynaptic character of the synapses entered into by the reticulospinal neurites. The configuration of axonal branching at the level of the lesion has led these researchers to comment that the paths taken by the regenerating neurites seem "due to local interactions between a growing tip and its immediate environment, rather than on a condition imposed on the cell as a whole." Examination of the scar tissue at the level of the lesion revealed "proliferating loosely aggregated ependymal cells." Nordlander and Singer, on the basis of similar findings in the newt, proposed earlier that extracellular channels created by ependymal cells may serve to guide regenerating neurites. Wood and Cohen suggest that "the ability to follow growth and synaptic regeneration in identified reticulospinal neurons of the lamprey may permit this preparation to serve as a model for examining the cellular factors concerned with functional recovery of the injured vertebrate central nervous system."

VI. PAIN

Chronic pain represents one of the most devastating disease entities which takes its toll in unmeasurable suffering and in extensive loss in productivity. Although acute pain may be considered a warning signal of bodily danger, chronic pain may be caused by a wider variety of insults from original but long-healed injury to small strokes in vital areas of the brain. The cost of chronic pain is massive and in inverse proportion to the amount of research being carried out.

The Stroke and Trauma Program issued an RFA indicating its interest in pain and soliciting high quality applications. Among the various applications received were three for the establishment of chronic pain centers, one of which was considered highly meritorious and has resulted in the funding of a project granted the University of Washington. It is the intention of STP to increase the level of pain support through the encouragement of high quality applications from innovative and dedicated investigators. Greater attention will be paid toward understanding the epidemiologic aspects of pain in the application through applied and clinical research of rapidly developing pain receptor and opiate receptor research. Detailed clinical investigation will be required to evaluate new and emerging therapeutic approaches and develop the necessary support systems.

CONTRACT NARRATIVE
Stroke and Trauma Program, NINCDS
October 1, 1979 -- September 30, 1980

Institutions

University of Rochester (N01-NS-8-2385)
North Carolina Heart Association (N01-NS-8-2386)
University of Oregon Health Sciences Center (N01-NS-8-2387)

Title: Comprehensive Stroke Center

Contractor's Project Directors: John H. Feibel, M.D. (Univ. of Rochester)
Paul E. Hirschauer (North Carolina Heart Assoc.)
Frank M. Yatsu, M.D. (Univ. of Oregon)

Current Level of Support: $478,100 (UR)
570,900 (NCHA)
497,300 (UOHSC)

Objectives: The objectives of these centers are to:

a. Conduct a program of applied clinical research in which fundamental advances are utilized in the development of specific approaches for the prevention, diagnosis and management of cerebrovascular disorders.

b. Develop integrated and coordinated community resources to evaluate the results of research on the prevention, diagnosis, and treatment of cerebrovascular disorders.

c. Demonstrate to physicians, other professionals and the public, by a broad public education program, the significant advances in cerebrovascular research and management.

Major Findings and Proposed Course:

1. North Carolina Heart Association

The Comprehensive Stroke Center Program in North Carolina is engaged in a community based effort to improve the in-hospital care of stroke patients and to provide more extensive post-hospital services. It is being conducted in three groups of counties in the southeast portion of the state, an area which is underserved by sophisticated medical expertise. By measuring the outcome of stroke patients in these three different groupings in a before and after algorithm, the effect of the program is being evaluated. All hospitals in 15 counties are now collecting data on stroke patients. The intensive treatment program has been implemented in two groups of hospitals with the third group scheduled for the Fall of 1980. Follow-up data are being collected by Home Health Agencies in the 15 counties after the patient has been discharged from the hospital. Stroke teams and other allied and medical health personnel are continuing to receive professional education from staff of the Comprehensive Stroke Program. Community Stroke Councils have been organized to develop and implement stroke prevention activities.

2. University of Rochester Stroke Center

   This Center is located in Monroe County, New York, the major city of which is Rochester. It includes all the community hospitals and health services with the focus at Strong Memorial Hospital. The benefits of the program are being seen in terms of increased physician and patient interest as well as an increase in cooperation from health care professionals dealing with stroke patients. The staff is continuing their outreach into nursing homes, hospitals, and community agencies on behalf of stroke patients.

3. The University of Oregon Health Sciences Center

   The Comprehensive Stroke Center in Oregon has been organized around four projects: Education, Epidemiology and Preventive Medicine, Clinical Research, and Rehabilitation. Currently the emphasis is on the rehabilitation and clinical research aspects. Stroke rehabilitation teams have been organized by the Center to work in rural locales which lack resources and trained personnel. They are providing rehabilitation for stroke patients in the areas of nursing care, and physical and occupational therapy. Protocols for the treatment of acute stroke with barbiturates and aminophylline have been developed and implemented. Studies on cognitive and neuropsychological defects associated with strokes are continuing.

Significance to NINCDS Program and Biomedical Research: As research in the Stroke Clinical Research Centers has progressed, questions have arisen regarding the applicability of their efforts. Do any of the techniques developed at a particular clinical research center reach the surrounding community hospitals? If so, does their application there produce the same results as it does at the Center? Does the presence of a Center affect the distribution of care of the stroke community? Does the care given in the Center affect mortality or morbidity for a given type of stroke? Will intensive rehabilitation efforts help in some cases? The Comprehensive Stroke Centers are attempting to find answers to these questions.

Proposed Course: The three Centers have developed somewhat independent programs with a certain degree of overlap. During the third year the collection and analysis of patient data will be done in accordance with guidelines established jointly by the three Centers.

Contractor	Termination Date
University of Rochester	6/28/81
North Carolina Heart Association, Inc. (now Am. Heart Assoc., N.C. Affiliate, Inc.)	5/31/81
University of Oregon Health Sciences Center	6/14/81

During the forthcoming year a new RFP will be issued for the next phase of the Stroke Center Program in which highly qualified institutions will be supported to conduct carefully controlled comparative clinical trials in the treatment and evaluation of stroke patients.

CONTRACT NARRATIVE
Stroke and Trauma Program, NINCDS
October 1, 1979 -- September 30, 1980

Institutions

University of California, San Diego (N01-NS-9-2312)
Albert Einstein College of Medicine (N01-NS-9-2313)
University of Texas Medical Branch (N01-NS-9-2314)

Title: Establishment of a Comprehensive Central Nervous System Trauma Center

Contractor's Project Directors:	Lawrence Marshall, M.D. Kenneth Shulman, M.D. Robert G. Grossman, M.D.
Current Annual Level of Support:	$447,300 (UCSD) 766,600 (AECM) 504,300 (UTMB)

Objectives: The purpose of this program is to evaluate the availability and the efficacy of the care of patients with CNS trauma, and to develop guidelines for optimal care of these patients in the setting of their community resources. In conjunction with these broad goals, specific objectives will be to:

1. Develop coordinated community resources by means of which developments in CNS trauma research can be evaluated on a community basis.

2. Foster clinical research on improved diagnosis and treatment of patients with CNS trauma.

3. Bring results of research on CNS trauma rapidly and effectively to the general community and especially to those segments of the community with a high incidence of CNS trauma.

It is hoped that such a center could serve as a general guide to the development of improved facilities for patients with CNS injury in other communities with similar geographical and population characteristics.

Major Findings: The epidemiological and data collection and processing aspects have been further refined in an effort 1) to capture the most relevant information, 2) to allow comparable cummulative data to be derived from the several trauma centers, and, 3) to enable the most promising areas of clinical investigation to be explored. There has been further integration of regional hospital networks for referral of patients and data. Regional emergency services are being categorized and enhanced interactions fostered. The centers are working toward the development of general community awareness of the program and its goals. To help achieve the latter, several community advisory committees have been organized or are undergoing organization.

Significance to NINCDS Program and Biomedical Research: A survey of CNS trauma in the United States revealed approximately 400,000 new cases of head injury, severe enough to be hospitalized. Approximately one half of these cases were 24 years old or younger. Due to the youth of those incapacitated, the impact on national health and productivity is evident. Because of this, the NINCDS has had special interest in the problem of CNS trauma, and is supporting research, both in basic studies aimed at clarifying the pathophysiology of brain and spinal cord injury and in clinical studies designed to improve diagnosis and treatment, particularly in the period immediately following the injury. Through its programs of head injury and spinal cord injury research, information important to patient care is being obtained. New diagnostic techniques and new forms of treatment are being evaluated in specialized clinical research units. In view of the increasing amount of research in this field, it is now appropriate to evaluate this new information at the community level and to contribute to its utilization.

Proposed Course: It is expected that at least three years of support will be required to permit the acquisition of data, the evaluation of clinical interventions, and the establishment of fully operational trauma centers that can serve as research-service models for other communities.

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